The American Heart Journal

VOL. 13 MARCH, 1937 No. 3

Original Communications

THE VASCULAR COMPLICATIONS OF POLYCYTHEMIA*

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POLYCYTHEMIA vera was first described by Vaquez[34] in 1892. As early as 1903, Osler[22] described it as a new clinical entity and recognized the frequency with which vascular complications occurred. These vascular complications are largely the result of an increased tendency to thrombosis resulting from a slowed circulation[2, 11, 13] in a vascular bed which is distended by the greatly increased blood volume. Another important factor may be increase in the number of platelets, and an increase in the serum calcium, shown by Brown and Roth,[6] may be a contributory factor. It is also possible that the intima is injured by a disturbed blood supply to it, or from excessive wear and tear by a fluid of increased viscosity, which Oppenheimer[21] believed may facilitate the formation of premature arteriosclerosis. Such changes in the intima naturally encourage thrombosis. Furthermore, most patients with polycythemia are at the age when arteriosclerosis is common. As will be pointed out subsequently, thrombosis may occur in vessels in many parts of the body, such as in the peripheral, cerebral, coronary, portal, hepatic, mesenteric, and splenic blood vessels. Such complications in polycythemia vera may frequently be the cause of death.

Parkes-Weber[24] in 1922 and Harrop[15] in 1928 reviewed the literature extensively. We have reviewed the literature dealing with vascular complication subsequent to 1928 only. Thrombosis of part of the splenic artery is the commonest cause of pain in the upper left quadrant of the abdomen in the presence of polycythemia. It occurs in a considerable number of cases during the course of the disease or during treatment with phenylhydrazine, as pointed out by Giffin,[12] and is a common finding at necropsy. The severe pain of mesenteric thrombosis may simulate

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that of perforation of a viscus or that of cholecystic disease. Adams,[1] in a report of nine cases, described three in which intraabdominal thrombosis was noted; one patient underwent an exploratory operation twice for severe abdominal pain. Nothing was found but an acutely enlarged spleen, which probably was the result of splenic infarction. Roch and Epstein[28] reported a case of thrombophlebitis of the gastroepiglottic veins that simulated perforation of the stomach. Patients suffering from thrombosis of the portal or mesenteric veins frequently have ascites and enlargement and cirrhosis of the liver. Other reports dealing with thrombosis of intraabdominal vessels have been made by A. Jacobi,[17] Oppenheimer,[21] Cole,[8] Singer,[30] Cory[9] and Parkes-Weber.[25] In this connection, the suggestion first proposed by Lommel,[19] that stagnation of the portal circulation as a result of portal thrombosis may be the primary cause of polycythemia vera, should be mentioned. It is believed by most writers that ordinarily the causal relationships are reversed, and that thrombosis, when it occurs, is the result rather than the cause of polycythemia. However, Tumen[33] reported a case of polycythemia in which the patient was a negress. In this case there was occlusion of the inferior vena cava by a large uterine fibroid; he attributed the polycythemia to this occlusion. There was no evidence, however, of a causal relationship in this report, as the patient died soon after the operation, before observation could be made relative to the permanency of the polycythemia. Poll[27] reported a case in which the clinical findings were of pulmonary thrombosis only; the patient was a woman, aged fifty-four years, who was receiving treatment for polycythemia vera and coincidental pyelonephritis. In this case, the polycythemia vera long preceded the pulmonary thrombosis, and in no sense was caused by it.

Coronary thrombosis does not appear to occur with as great frequency as does thrombosis in vessels of other organs. This may be due to the fact that stagnation is not as marked in the vessels of a muscular organ in active contraction as it is in vessels of a less active organ, even though other factors that increase the liability to clotting are operative. Oppenheimer[21] reported a case in which the clinical studies revealed coronary thrombosis with a pericardial rub, fever, leucocytosis, and electrocardiographic changes. Parkes-Weber[25] reported a case in which gout, migraine, and intracardiac thrombosis were observed. Christian,[7] Sloan,[31] and Adams,[1] in separate reports, have pointed out the frequency with which cerebral vascular accidents are the cause of neurological symptoms, and Elschnig and Nonnenbruch[10] reported a case in which embolism of the central artery of the retina occurred simultaneously with a cerebral vascular accident. Migrating phlebitis, according to Lüdeke,[20] frequently is a complication of polycythemia vera. He reported sixty cases of phlebitis, in ten of which there were definite evidences of polycythemia. Brown and Giffin[5] have pointed out the frequent occurrence

of complications in the peripheral vascular system. They reviewed 100 cases of polycythemia vera that had been observed at the Mayo Clinic from 1912 to 1929, and placed the cases with peripheral vascular complications into groups in which the symptoms simulated arteriosclerosis obliterans, thromboangiitis obliterans, erythromelalgia, and Raynaud's disease. Brown[3] emphasized that erythromelalgia may be a symptom of polycythemia vera, and Horton and Brown[16] described the association of thromboangiitis obliterans and polycythemia. It is interesting to note that Osler[23] in 1908 mentioned the fact that the "red painful neuralgias" of the extremities which occur in cases of polycythemia vera may simulate erythromelalgia. Other recent reports of peripheral vascular complications have been made by Oppenheimer,[21] Jacobi,[18] Sloan,[32] and Griffith.[14]

Geisbok's disease, or polycythemia hypertonica, has been considered to be a complication of polycythemia vera, but Rowntree, Brown, and Roth[29] believed it to be a coincidental association of hypertension and polycythemia vera. Peacock[26] found that in polycythemia vera the average values for the blood pressure of patients of different ages were not significantly raised above normal, and that there was no correlation between increased blood pressure and blood volume. Brown and Giffin[4] reached a similar conclusion in a study made in 1926.

Hemorrhage occurs often in polycythemia vera; epistaxis and excessive hemorrhage following alveolectomy are common. Hemorrhage from dilated esophageal veins may occur. That hemorrhage should be common in a disease in which the tendency to clotting is increased seems paradoxical until it is realized that great distention occurs in the vascular bed, which undoubtedly is the most important factor in the causation of hemorrhages. Harrop[15] believed that there may be a variability in the tendency to clotting, and that at one time a tendency to clotting, and later a tendency to hemorrhage, may be observed in the same case.

In our study we have followed the criteria of Rowntree, Brown, and Roth.[29] In a study of the volumes of whole blood and of blood corpuscles, they found normal standards of 80 to 100 c.c. for each kilogram of body weight, and a hemacrit value of 40 to 48. In polycythemia vera the blood volume, the volume percentage, the viscosity of the blood, the value for the hemoglobin, and the number of erythrocytes in each cubic millimeter of blood are increased. Similar changes are present in relative polycythemia, except that the blood volume is approximately normal.

POLYCYTHEMIA VERA

In the seven years between Jan. 1, 1929, and Jan. 1, 1936, ninety-eight cases of polycythemia vera were observed at the Mayo Clinic. In thirty-three, or approximately 34 per cent, vascular complications occurred. For purposes of study, these vascular complications were

classified as follows: with intraabdominal thrombosis, six cases; with diseases of the coronary arteries, five; with diseases of the cerebral vessels, six; with peripheral occlusive vascular disease, seven; with erythromelalgia and burning paresthesia, eight; and with vasospastic phenomenon, one case.

Polycythemia Vera With Intraabdominal Thrombosis.—Although intraabdominal thrombosis was suspected in all of these six cases, it was proved in only two (by necropsy in Case 3 and by operation in Case 5), as opportunities for direct observation of the intraabdominal vessels by necropsy or operation was afforded in none of the remaining cases in this series. However, the clinical history and findings were highly suggestive of intraabdominal thrombosis in all (Table I). Additional vascular complications were noted in Case 1 (erythromelalgia) and in Case 4 (hemiplegia).

CASE 3.—A white woman, aged fifty-four years, was admitted to the clinic May 13, 1934, because of an enlargement of the spleen which had been present for five years. Ten months prior to her admission, she had received treatment elsewhere for polycythemia vera; this treatment had consisted of the application of roentgen therapy to the long bones. Ten days prior to her admission, a severe pain had occurred in the left lower quadrant of the abdomen, and two days later rapidly increasing anasarca had developed.

Examination of the patient at the clinic revealed ascites, slight icteric tinting of the conjunctiva, and enlargement of the liver and spleen. There was acute tenderness over the spleen and in the left lower quadrant of the abdomen. The value for the blood pressure in millimeters of mercury was 170 for the systolic and 110 for the diastolic, and pitting edema of the legs was noted. Examination of the retinal veins revealed marked engorgement and cyanosis. The results from study of the blood may be noted in Table I. The blood volume for each kilogram of body weight was obviously low because of increased weight of the body due to ascites and edema. Urinalysis revealed a large amount of albumin, a few casts, and pus cells. The concentration of urea in the blood was normal, and that of bilirubin was 4.0 mg. per 100 c.c. of serum. Following a Congo red test, there was a 28 per cent loss of dye from the blood stream in one hour, which excluded amyloidosis as the cause of the albuminuria.

On May 16 abdominal paracentesis was carried out, and 1,450 c.c. of clear, straw-colored fluid was removed before it became bloody, at which time the operation was terminated. Injection of the ascitic fluid into a guinea pig did not produce evidence of tuberculosis. In spite of the administration of diuretics and supportive treatment, the condition of the patient became gradually worse, and she died May 20.

At necropsy there was 700 c.c. of hemorrhagic amber-colored fluid in the abdomen. The heart was enlarged, and weighed 325 gm. (calculated normal weight, 250 gm.), and there was generalized sclerosis of the coronary arteries. The spleen was enormously enlarged; it weighed 1,576 gm. (calculated normal weight, 150 gm.), and microscopic examination revealed chronic fibrous splenitis with reticular proliferation. Several branches of the splenic artery were plugged with organizing thrombi, and there were many small splenic infarcts. The liver weighed 2,560 gm. (calculated normal weight, 1,600 gm.), and canalized thrombosis of the hepatic veins was noted. Microscopic examination of the liver revealed marked acute passive congestion and

TABLE I

POLYCYTHEMIA VERA ASSOCIATED WITH INTRAABDOMINAL THROMBOSIS

CASE	AGE (YEAR) AND SEX	SYMPTOMS OF INTRAABDOMINAL THROMBOSIS	DIAGNOSIS	STUDIES OF THE BLOOD				
				HEMOGLOBIN, GM. PER 100 C.C. OF BLOOD	ERYTHROCYTES, MILLIONS, IN EACH C.MM. OF BLOOD	HEMACRIT READING	VISCOSITY OF WHOLE BLOOD	VOLUME OF BLOOD IN C.C. FOR EACH KG. OF BODY WEIGHT
1	F 61	Recurrent episodes of pain in upper part of abdomen associated with emesis of blood	Intraabdominal thrombosis?*	20.3	6.63	71	11.2	110
2	F 41	Pain in splenic region	Splenic thrombosis?	19.1	9.0	69	11.6	131
3	F 54	Ascites, edema of legs, hematuria	Thrombosis of hepatic veins†	17.5	6.03	66	7.0	117
4	M 42	Ascites and abdominal pain	Mesenteric thrombosis?‡	18.5	5.30	60	6.7	102
5	M 26	Severe abdominal pain projected to back	Mesenteric thrombosis proved by operation elsewhere	17.8	6.62	60	9.0	141
6	F 30	Ascites, nausea and vomiting	Portal thrombosis? Cirrhosis of liver?	17.6	5.82	56	6.9	119

*Erythromelalgia of right foot.
†Diagnosis made at necropsy.
‡Left hemiplegia.

TABLE II

POLYCYTHEMIA VERA WITH DISEASE OF CORONARY ARTERIES

CASE	AGE (YR.) AND SEX	SYMPTOMS OF CORONARY ARTERIAL DISEASE	DIAGNOSIS	STUDIES OF THE BLOOD				
				HEMOGLOBIN, GM. PER 100 C.C. OF BLOOD	ERYTHROCYTES, MILLIONS, IN EACH C.MM. OF BLOOD	HEMACRIT READING	VISCOSITY OF WHOLE BLOOD	VOLUME OF BLOOD IN C.C. FOR EACH KG. OF BODY WEIGHT
7	F 61	Pain in precordium and numbness of left arm	Angina pectoris*	16.9	4.5	50		71
8	F 69	Dyspnea on exertion; swelling of legs	Arteriosclerotic heart disease with congestive failure*†	17.2	5.8	59	7.0	108
9	M 53	Bilateral pain in thorax with extension down left arm, occurrence with exercise or rest; relief with amyl nitrite and nitroglycerin	Coronary sclerosis with angina pectoris‡	22.1	5.4	74	10.2	141
10	M 47	Pain in left side of thorax followed by dyspnea and ascites	Thrombosis of coronary arteries diagnosed elsewhere*	8.5	4.5		3.1	79.6
11	F 44	Exhaustion	Hypertensive and arteriosclerotic heart disease with auricular fibrillation	16.9	5.6	59	8.8	114

*Polycythemia diagnosed and treated elsewhere.
†Arteriosclerotic occlusion of dorsalis pedis arteries bilaterally.
‡Thrombosis of the coronary artery discovered at necropsy.

marked congestion in the sinusoids, with central atrophy of the hepatic cords. Many intrahepatic vessels were occluded by well-organized thrombi. The marrow of the ribs was packed with erythrocytes, but otherwise appeared normal.

Plycythemia Vera With Disease of the Coronary Arteries.—Two of the patients in this series had angina pectoris, and one of these had evidence of myocardial infarction which was discovered at necropsy (Table II). In one case, thrombosis of a coronary artery was diagnosed elsewhere; in one case there was evidence of arteriosclerotic heart disease; and in another case there was evidence of arteriosclerotic and hypertensive heart disease. In one case, an additional complication of absence of pulsations in the dorsalis pedis arteries was noted bilaterally.

CASE 9.—A white man, aged fifty-three years, was admitted to the clinic June 30, 1932, because of headaches, intolerance to heat, nervousness which had been present for the past four years, and episodes of severe substernal pain which had been present for the preceding four or five weeks. The pain, which had been severe and had occurred even while the patient was at rest, often during the day, had been situated in the left anterior and posterior walls of the thorax and had extended down the left arm.

Examination of the patient at the clinic revealed evidence of polycythemia. Several small adenomas were palpable in each lobe of the thyroid gland, and the spleen was enlarged and extended approximately 2½ inches (6.25 cm.) below the left costal margin. The results of studies of the blood may be observed in Table II. A roentgenogram of the thorax revealed that the heart was enlarged and that there was congestion at the bases of both lungs. An electrocardiogram revealed the presence of sinus tachycardia with a rate of 96 beats each minute, left ventricular preponderance, inverted T-wave in Lead III, diphasic T-wave in Leads I and II, exaggerated P-waves, and notched QRS complexes in Leads II and III. A diagnosis of polycythemia vera and angina pectoris was made.

The patient was treated in the hospital with phenylhydrazine hydrochloride. The attacks of angina, which occurred with increasing frequency, were completely relieved by the administration of amyl nitrite and nitroglycerin, and the patient took about forty 1/100 gr. (0.0006 gm.) tablets of nitroglycerin daily. On July 25, after the patient had received 4.5 gm. of phenylhydrazine, the erythrocytes numbered 4,300,000 per cubic millimeter of blood; the hematocrit reading was 43.7 volume per cent; and the viscosity was 5.4. The patient died suddenly.

Necropsy revealed enlargement of the liver and spleen. Generalized fibrous scarring of the myocardium and generalized sclerosis of the coronary arteries were present. A thrombus of recent origin was found in the left coronary artery.

Polycythemia Vera With Symptoms of Cerebrovascular Disease.—Of the six patients in this group, five had histories suggestive of, or clinical evidence of, cerebrovascular hemorrhage or thrombosis. In one case the clinical history suggested spasm of a cerebral artery, although hemorrhage or thrombosis could not be excluded. In another case the additional vascular complication of thrombophlebitis affecting the left leg was present (Table III).

CASE 16.—A man, aged forty-four years, was admitted to the clinic Aug. 20, 1930, because of weakness, loss of deep sensibility and coordination of the muscles of the

TABLE III

POLYCYTHEMIA VERA WITH SYMPTOMS OF DISEASE OF CEREBRAL VESSELS

CASE	AGE (YR.) AND SEX	SYMPTOMS OF DISEASE OF CEREBRAL VESSELS	DIAGNOSIS	STUDIES OF THE BLOOD				
				HEMOGLOBIN, GM. PER 100 C.C. OF BLOOD	ERYTHROCYTES, MILLIONS, IN EACH C.MM. OF BLOOD	HEMACRIT READING	VISCOSITY OF WHOLE BLOOD	VOLUME OF BLOOD IN C.C. FOR EACH KG. OF BODY WEIGHT
12	M 64	Attacks of unconsciousness, and of numbness of right hand	Cerebral arteriosclerosis with thrombosis of left parietal region	18.8	4.89	63		133
13	M 47	Paralysis of right side of face and paresthesia of left side of face lasting one-half day	Cerebrovascular spasm	23.1	7.85		14.2	
14	M 54	Aphasia and right hemiplegia	Cerebrovascular thrombosis or hemorrhage*	21.6	7.24	76	12.8	216
15	M 48	Sudden paresthesia of left hand followed by partial paralysis of left hand	Cerebrovascular thrombosis or hemorrhage	22.1	6.93	80	9.2	147
16	M 44	Numbness and weakness of right hand and partial aphasia	Arterial thrombosis or hemorrhage in the left temporoparietal area	25.0	6.45	73	10.6	139
17	M 60	Paralysis of right arm and hand, and aphasia; right homonymous hemianopia	Cerebrovascular hemorrhage or thrombosis	20.6	6.35	64	7.4	110

*Thrombophlebitis of the left leg.

right hand and forearm, which had been present for the past ten months, and on account of difficulty in speaking and poor memory, which had been present for the past four months.

Examination of the patient revealed evidence of polycythemia. The spleen and heart were enlarged. Results of studies of the blood may be noted in Table III. Examination of the eyegrounds revealed cyanotic and engorged veins. Roentgenograms of the thorax and head were normal. The Wassermann reaction of the blood was normal, and urinalysis did not reveal any abnormality. On neurological examination, motor and sensory aphasia, marked alexia and agraphia, and some apraxia were noted; the right arm was weak. The diagnosis was cerebral softening in the left parietotemporal region, caused by a vascular lesion. The patient was treated in the hospital with phenylhydrazine hydrochloride. During treatment the weakness of the right hand and the aphasia increased. Weakness of the right leg and a positive Babinski sign developed on that side. When 3 gm. of phenylhydrazine had been given, the concentration of hemoglobin was 95 per cent; erythrocytes numbered 6,920,000 per cubic millimeter of blood; the hematocrit reading was 60 per cent; and the viscosity of the blood was 8.4. The patient became despondent and refused to stay longer. On dismissal, there were marked paralysis of the right hand and arm, weakness of the right leg, and both motor and sensory aphasia.

Polycythemia Vera With Occlusive Vascular Disease of the Legs.—Of the seven patients in this group, four had phlebitis, and three had evidence of chronic occlusive arterial disease indistinguishable from arteriosclerosis obliterans. In addition, one patient had had symptoms of erythromelalgia, and one had hypertension and cardiac enlargement (Table IV).

Case 23.—A white man, aged sixty-one years, was admitted to the clinic Nov. 27, 1930. He had suffered for the past five years from burning distress over the heads of the metatarsal joints when walking, which had not been relieved by rubber pads or arch supports. Four years before his registration at the clinic he had received an injection of calcium chloride into one of the veins of his right leg. The injection had been followed in an hour by numbness and whiteness of the right foot and severe pain that had extended from the foot to the knee. Gangrene had developed, and amputation in the region of the middle of the thigh had been necessary. Healing had occurred promptly. Three years before he came to the clinic, he had injured the fifth toe of the left foot; infection and gangrene had set in, which had necessitated amputation of this toe. For the past year, there had been persistent coldness and burning in the sole of the left foot. Four months prior to his admission, the big toe had become blue and cold, but after a month the normal color had returned. Two weeks previous to examination at the clinic, pain and cyanosis had developed at the tip of the second left toe, and on admission the pain in this toe was continuous.

Examination of the patient revealed evidence of polycythemia. The value for the blood pressure expressed in millimeters of mercury was 160 for the systolic and 100 for the diastolic; the heart was enlarged. There was reddish blue discoloration of the tissues of the first and second left toes, and both were cold. The left fifth toe had been amputated previously. Pulsations were absent in the left dorsalis pedis artery and diminished in the posterior tibial artery. The results from study of the blood may be noted in Table IV. Roentgenological examination revealed evidences of calcification of the arteries of the left leg. The flocculation test for syphilis gave negative results. Urinalysis revealed the presence of moderate albuminuria. The concentration of urea in the blood was normal. The diagnosis was polycythemia vera and arteriosclerosis obliterans.

TABLE IV

POLYCYTHEMIA VERA WITH OCCLUSIVE VASCULAR DISEASE OF LEGS

CASE	AGE (YR.) AND SEX	SYMPTOMS OF VASCULAR DISEASE OF LEGS	DIAGNOSIS	STUDIES OF THE BLOOD				
				HEMOGLOBIN, GM. PER 100 C.C. OF BLOOD	ERYTHROCYTES, MILLIONS, IN EACH C.MM. OF BLOOD	HEMACRIT READING	VISCOSITY OF WHOLE BLOOD	VOLUME OF BLOOD IN C.C. FOR EACH KG. OF BODY WEIGHT
18	F 53	Thrombosis, tenderness and redness of varicosities	Thrombosis in varices	21.3	6.72	76	13.6	261
19	F 53	Edema of legs following left nephrolithotomy; pain in thorax	Bilateral thrombophlebitis; pulmonary embolus with infarction*	15.9	7.52	59	7.6	98
20	M 68	Bilateral claudication in calf of each leg	Arteriosclerosis obliterans with bilateral occlusion of popliteal, dorsalis pedis and posterior tibial arteries	20.9	6.78	68		120
21	F 62	Ulcer of left leg over first metatarsal phalangeal joint; intermittent claudication in calf of left leg; pallor and cyanosis of thumb and first two fingers of left hand	Chronic arterial disease with occlusion of left dorsalis pedis and posterior tibial arteries and superficial venous thrombosis; chronic arterial disease with occlusion of left radial artery	21.0	8.77	75	16.0	186
22	F 57	Pain in right popliteal space	Popliteal thrombophlebitis proved surgically	15.2	4.23	46	5.8	124
23	M 61	Pain, cyanosis and gangrene of left second toe; amputation of leg necessary	Occlusive arterial disease†	16.6	6.44	75	12.2	113
24	F 47	Pain in calves of legs; swelling of legs	Bilateral thrombophlebitis‡ Hypertension and cardiac enlargement	18.0	6.5	68	8.6	114

*Polycythemia vera diagnosed and treated elsewhere.
†Previous episode (three months) of erythromelalgia.
‡Patient receiving phenylhydrazine.

Phlebotomy was performed several times to reduce the blood volume, and treatment was carried out to increase circulation to the leg. However, there was evidence of progressive diminution in arterial circulation, and gangrene of the second toe developed. Amputation of the toe was not followed by healing, and amputation of the leg was necessary, following which healing occurred promptly.

Polycythemia Vera With Symptoms of Erythromelalgia and Burning Paresthesia.—According to our criteria, the diagnosis of erythromelalgia is justified only when sensations of burning in the feet are associated with actual increase in the temperature of the skin. When subjective burning occurs without increase in cutaneous temperature, we consider the correct diagnosis to be paresthesia. Following these criteria, there were three cases of erythromelalgia and four cases of paresthesias in this series (Table V). In Case 32, erythromelalgia probably was present, since the patient said there was objective evidence of increase of temperature of the skin, but we could not demonstrate this with a thermometer. One patient had vascular complications of gastric hemorrhage and bilateral thrombophlebitis of the legs (Case 28); another had angina pectoris and phlebitis in varices (Case 31); and a third gave a history of phlebitis and absence of pulsations in the left posterior tibial artery (Case 32).

Case 25.—A Russian Jew, aged forty-seven years, was admitted to the clinic July 15, 1931, because of sharp, stabbing pain in the plantar surfaces of both feet and in the distal half of the left foot; this pain came in attacks; and there was complete relief between attacks. Elevation of the feet and application of cold did not produce any relief, and the patient had not noted associated changes in color or temperature. Symptoms of peptic ulcer had been present.

Examination of the patient at the clinic revealed an enlarged spleen, marked erythrosis of the mucous membranes and hands, engorged retinal veins, and diminished pulsation of both dorsalis pedis arteries. Results of studies of the blood may be noted in Table V. Roentgenological examination revealed evidence of a duodenal ulcer. Study of the temperature of the skin of the painful areas during an attack showed an increase of about 2° C.

The duodenal ulcer was treated medically, and phenylhydrazine hydrochloride was given for the polycythemia. Excellent response of the blood to phenylhydrazine occurred, and, as the blood returned almost to normal, the distress in the feet disappeared.

The patient returned to the clinic April 26, 1933. He had not followed instructions relative to the use of phenylhydrazine, and the polycythemia and erythromelalgia had recurred. Treatment of the polycythemia with phenylhydrazine was again instituted with good results, but the distress in the feet persisted. Subsequently, the polycythemia was well controlled with phenylhydrazine, and the distress in the patient's feet disappeared shortly after his dismissal from the clinic May, 1933.

Polycythemia Vera With Vasospastic Phenomena.—Case 33 was the only case in this category. In this case there was evidence of auricular fibrillation, which apparently was the result of arteriosclerotic heart disease. We hesitate to indicate that this case is representative of true Raynaud's disease, since the patient was a man, and since only one phase, color reaction, namely cyanosis, had occurred. It is probable

TABLE V

POLYCYTHEMIA VERA WITH SYMPTOMS OF ERYTHROMELALGIA AND WITH BURNING PARESTHESIA

CASE	AGE (YR.) AND SEX	SYMPTOMS OF ERYTHROMELALGIA	DIAGNOSIS	STUDIES OF THE BLOOD				
				HEMOGLOBIN, GM. PER 100 C.C. OF BLOOD	ERYTHROCYTES, MILLIONS, IN EACH C.MM. OF BLOOD	HEMACRIT READING	VISCOSITY OF WHOLE BLOOD	VOLUME OF BLOOD IN C.C. FOR EACH KG. OF BODY WEIGHT
25	M 45	Episodes of severe pain in both feet; temperature of skin of feet increased during pain	Erythromelalgia	19.9	6.05	66	11.2	127
26	M 54	Burning pain in right toe with exercise; no increase in temperature of skin	Burning paresthesia	18.9	8.12	66	9.0	115
27	M 55	Episodes of burning involving distal half of right foot and left great toe; elevation of cutaneous temperature during attacks	Erythromelalgia	19.2	5.18	63	10.6	109
28	F 70	Burning sensation of feet	Burning paresthesia*	23.9	8.2	74	14.6	172
29	F 49	Attacks of burning associated with elevation of temperature of skin involving hands and feet	Erythromelalgia	18.2	5.28	56	7.0	148
30	M 59	Burning sensation in soles of feet; no increase in temperature of the skin	Burning paresthesia	19.2	6.81	64	10.4	184
31	M 58	Episodes of burning in left foot not associated with increased cutaneous temperature	Burning paresthesia†	21.7	7.44	74	14.8	132
32§	M 38	Episodes of burning in left foot; not always associated with elevation of cutaneous temperature	Erythromelalgia?‡ Paresthesia?	20.5	6.53	60	8.4	109

*Gastric hemorrhage; bilateral thrombophlebitis of legs.

†Angina pectoris; history of phlebitis affecting varices.

‡Left posterior tibial artery occluded, history of phlebitis; thromboangiitis obliterans (?).

§Case 33 is not included in the tables but is discussed in the text.

that the patient had an organic disease of the digital arteries, and, unless this possibility is excluded by arteriography, the diagnosis of Raynaud's disease is not justified.

VASCULAR COMPLICATIONS OF "RELATIVE POLYCYTHEMIA"

The term "relative polycythemia" refers to a condition in which the status of the blood is similar to that in polycythemia vera, except that the blood volume is within normal limits. This condition has been noted in some cases of Raynaud's disease and thromboangiitis obliterans by Brown and Giffin,[5] Horton and Brown,[16] and Rowntree, Brown, and Roth.[29] Harrop[15] cited two cases reported by Wright in which cerebrovascular hemorrhage or thrombosis affected patients who had relative polycythemia: a child, aged twelve years, had spastic hemiplegia which had followed convulsions when she had had measles at the age of four years. Cyanosis, clubbing of the fingers, and evidence of incomplete aeration of blood in the lungs were present. An infant, aged twenty months, had a paralyzed right arm and evidence of congenital stenosis of the pulmonary arteries.

Relative polycythemia was diagnosed thirty-five times at the clinic during a period of seven years (from Jan. 1, 1929, to Jan. 1, 1936). Doubtless many more cases were observed, but ordinarily such a diagnosis is made only when the condition is of primary interest. In many conditions, such as emphysema, studies for polycythemia such as determination of blood volume are not made because the presence of polycythemia is of little practical importance in the condition.

In twelve of the cases in which relative polycythemia was determined, there was evidence of vascular lesions. In none of these cases was polycythemia marked (Table VI). The highest erythrocyte count was 5.7 millions in each cubic millimeter of blood, and the most abnormal volume percentage of cells in the blood was 63. In several cases the increase in the number of erythrocytes, in the hematocrit readings, and in the viscosity of the blood was only minimal, exceeding normal by very little. The results probably represent phenomena attributable to simple concentration of the blood from a variety of causes. However, we feel there is justification for referring to these cases since polycythemia of some degree was present in all. There were five cases of thromboangiitis obliterans, two cases of arteriosclerosis obliterans, and one case each of erythromelalgia, cerebral hemorrhage or thrombosis, vasospastic neurosis, thrombophlebitis, and thrombosis of the inferior epigastric and portal veins.

COMMENT

Inquiry is pertinent as to whether the coexistence of polycythemia vera and vascular complications is incidental or is representative of a cause-and-effect relationship. Since both polycythemia vera and the

TABLE VI

VASCULAR COMPLICATIONS OF RELATIVE POLYCYTHEMIA

CASE	AGE (YR.) AND SEX	SYMPTOMS OF VASCULAR DISEASE	DIAGNOSIS	STUDIES OF THE BLOOD				
				HEMOGLOBIN, GM. PER 100 C.C. OF BLOOD	ERYTHROCYTES, MILLIONS, IN EACH C.MM. OF BLOOD	HEMACRIT READING	VISCOSITY OF WHOLE BLOOD	VOLUME OF BLOOD IN C.C. FOR EACH KG. OF BODY WEIGHT
34	M 49	Intermittent claudication; superficial phlebitis*	Thromboangiitis obliterans	15.9	5.29	51	6.8	
35	M 57	Superficial phlebitis; stasis dermatitis*	Thromboangiitis obliterans	18.2	4.54	51	5.3	63
36	M 46	Intermittent claudication; recurrent episodes of discoloration and pain involving right fifth toe and the heel*	Thromboangiitis obliterans	17.4	5.71	58	7.0	72
37	M 52	Intermittent claudication*	Thromboangiitis obliterans	17.8	4.32	57		73
38	M 53	Intermittent claudication; gangrene of toe, phlebitis*	Thromboangiitis obliterans	19.5	5.14	63	8.0	88
39	M 54	Burning sensation in both feet associated with increase in temperature of skin	Erythromelalgia	18.6	4.50	53		72

TABLE VI—CONT'D

40	F 51	Episodes of burning of soles of feet; right hemiplegia, apraxia and agnosia†	Left cerebral arterial hemorrhage or thrombosis; paresthesia of feet	19.2	5.11	58	5.8	88
41	M 61	Intermittent color changes of fingers and toes varying from cyanosis to pallor	Vasospastic neurosis simulating Raynaud's disease‡	16.9	5.00	50	6.7	
42	M 45	Edema of left leg and of right leg nine months later	Thrombophlebitis	16.9	5.20	60		
43	F 62	Gangrene of toes	Arteriosclerosis obliterans?; peripheral arteries pulsating normally	16.4	5.70	49	6.7	
44	M 59	Intermittent claudication in right calf; severe prolonged attack of pain in the thorax	Arteriosclerosis obliterans; coronary sclerosis with myocardial infarction	15.2	5.09	50	7.4	92
45	F 19	Ascites, enlarged liver and spleen and numerous gastric hemorrhages	Cirrhosis of liver, thrombosis of portal and inferior epigastric veins observed at necropsy§	13.8	5.30	55		108

*Occlusion of some arteries in legs.
†Patient underwent venesection and roentgen ray therapy elsewhere; she may have had polycythemia vera.
‡Some evidence of myelogenous leucemia.
§Diagnosis not absolute; polycythemia vera with secondary venous thrombosis or cirrhosis of the liver with secondary polycythemia.

vascular diseases considered usually affect elderly individuals, it might be assumed that mere chance was responsible for two conditions affecting the same person. However, approximately one-third of all of our patients who had polycythemia vera had vascular diseases, which fact indicates that polycythemia was responsible for the vascular diseases in most instances since the latter affect a much smaller proportion than one-third of all our patients of similar ages and sex. Moreover, this hypothesis is logical, as the conditions in the blood are those which produce an increased tendency to thrombosis. The situation is not so clear in relative polycythemia, in which the disturbances in the blood are frequently minimal. If the records of all cases in which the changes in the blood were no more marked than they were in the present series of cases were available for study, it would doubtless be found that the percentage of cases with vascular complications would be small when compared with that in cases of polycythemia vera. It is probable, but by no means certain, that the changed status of the blood is not responsible for the vascular lesions in the majority of cases of relative polycythemia. For example, polycythemia is rare in thromboangiitis obliterans, and we view the relationship as one of coincidence rather than one of cause and effect. Naturally, the fundamental disturbance may, in some obscure manner, produce thromboangiitis obliterans and relative polycythemia. The observations just made regarding thromboangiitis obliterans apply to arteriosclerosis obliterans, and with less certainty to erythromelalgia and vasospastic neurosis. Phlebitis and cerebrovascular hemorrhage or thrombosis may have resulted directly from polycythemia, but we have no evidence that this is so. As indicated in Table VI, the diagnosis was not absolute in the case of thrombosis of the inferior epigastric and portal vessels.

Our study emphasizes two important points. It is advisable to treat polycythemia vera if for no other reason than to prevent vascular complications. If the many vascular diseases noted in our study are viewed with the suspicion that polycythemia vera exists, it will be found in at least a small percentage of cases. This is particularly true with regard to erythromelalgia, which is frequently a sign of polycythemia, as we have observed on numerous occasions. Furthermore, it appears that arteriosclerosis obliterans and thromboangiitis obliterans respond in a better manner to treatment if polycythemia which may be present is treated actively.

SUMMARY

Study of ninety-eight cases of polycythemia vera and thirty-five cases of relative polycythemia reveals that erythromelalgia, myocardial infarction, angina pectoris, occlusive disease of the peripheral arteries, cerebral hemorrhage of thrombosis, intraabdominal vascular thrombosis,

phlebitis, and vasomotor neurosis occur in about a third of the cases. Recognition of the relationships is important diagnostically and therapeutically.

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SIGNIFICANCE OF BLOOD VESSELS IN HUMAN HEART VALVES*

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DURING most of the eighty-four years in which reports have appeared on the problem as to whether blood vessels exist in normal human heart valves, a number of obstacles have interfered with its elucidation. As pointed out by Gross and Kugel,[1] one of the major difficulties lay in the fact that until recently no precise definition existed as to what constitutes the proximal limits of the several cardiac leaflets. As a consequence, when auricular myocardium was included as part of the auriculoventricular leaflets, these could be considered as possessing vasculature, since myocardium always contains blood vessels (Langer,[2] Dow and Harper[3]). On the other hand, when the leaflet (and ring) were considered as the purely fibroelastic structure distal to the myocardium, the existence of blood vessels in this site assumed an entirely different significance. This latter point, which has been the subject of an extensive controversy, will form the basis of this report. The topographical relations and limits of human heart valves, as defined by Gross and Kugel,[1] will be employed.

Another major obstacle in the problem has been the statement by Langer[2] that human embryonic heart valves contain myocardium and blood vessels and that these regress before birth. This assumption, which the present author has been unable to confirm, has offered the tempting explanation that blood vessels may exist in normal human valves as vestiges of the embryonic state.

A somewhat similar pitfall is the fact that several species of animals, e.g., ox, sheep, swine, dog, horse, etc., have blood vessels in normal valves. This suggests an all-too-facile analogy with the vessels at times found in human heart valves, an analogy which, as will be seen, is totally unjustified.

The most perplexing difficulty, however, lay in the fact that until recent years there were no means available for differentiating normal valves possessing certain involutionary changes (so-called tension changes), from the end-results of mild inflammatory lesions. As a consequence, most of the published reports have concerned themselves with improvements on injection methods, and scant attention was paid to careful histological examination of the tissues for the purpose of determining accurately their normality.

*From the Laboratories of the Mount Sinai Hospital, New York, N. Y.
Aided by grants from the Lucius N. Littauer and Walter W. Naumburg Funds.

The schools of thought in this field can be roughly divided into two groups. The first (Gerlach,[4] Luschka,[5] Kölliker,[6] Forster,[7] Henle,[8] Frey,[9] Rosenstein,[10] Sappey,[11] Krause,[12] Cruveilhier,[13] Cöen,[14] Bayne-Jones,[15] Kerr and Mettier,[16] Kerr, Mettier, and McCalla,[17] Wearn and his coworkers[18]) holds to the belief that blood vessels may exist in normal human heart valves, some authors considering these vessels to occur in the auriculoventricular as well as the semilunar valves, and others only in the former. The second group (Rokitansky,[19] Joseph,[20] Virchow,[21] Cadiat,[22] Langer,[2] Darier,[23] Königer,[24] Odinzow,[25] Nussbaum,[26] Tandler,[27] Dow and Harper[3]) considers that valves are normally nonvascularized and that, if blood vessels are found in them, they are due to an inflammatory process in the leaflets.

In previous publications, the author[28] with collaborators[29, 30] has adduced evidence which seemed to favor the belief that blood vessels may exist in a small percentage of normal human heart valves. In a report on 700 injected human hearts, Ritter, Gross, and Kugel[30] found blood vessels in 2 per cent of, what were considered at the time, intact valves. Although blood vessels were found in a considerable number of specimens (representing 18 per cent of this relatively large material), definite evidences of inflammation were found in a great majority of these. In later reports the author with collaborators[1, 31, 32] has expressed doubt as to the normality of any human heart valve possessing blood vessels.

The following observations summarize the evidence at present available in favor of the concept that blood vessels may exist in the fibroelastic portion of normal human heart valves:

1. Langer's claim[2] that human fetal valves possess myocardium and blood vessels.

2. The regular and sometimes constant occurrence of blood vessels in the normal heart valves of some animal species and the alleged similarity of these vessels to those found in human heart valves.

3. The demonstration of blood vessels in apparently normal human heart valves ranging from 2 per cent[30] to 74 per cent.[18] The increased incidence of blood vessels as demonstrated by more recent workers has been attributed to improvements in injection technic.

4. The apparent absence of clinical or pathological evidence indicating present or past inflammatory disease in these hearts.

5. The histological structure of the valvular vessels, i.e., the occurrence of muscular wall arteries and veins.[29]

6. The apparent topographical regularity of blood vessels found in human heart valves.[29, 30, 33]

7. The apparent nondependence of these vessels on valvulitis, inasmuch as the incidence of vascularization of the several valves does not parallel the incidence of inflammation in them (Wearn and his collaborators[18]).

As against the concept of the existence of vessels in the fibroelastic portion of normal human heart valves are:

1. The existence of normal hearts without evidence of blood vessels in the valves. The incidence of such normal hearts ranges, according to various authors, from 98 per cent to 26 per cent.

2. The extraordinarily frequent coexistence of valve inflammation (chiefly of the rheumatic variety) in the great majority of specimens showing valve vasculature.

3. The histological similarity of the vessels occurring in inflamed valves (and obviously resulting from the inflammation) with those found in supposedly normal valves.

4. The coexistence of myocardial fibers with blood vessels which seem to extend into the fibroelastic portion of the leaflets (Langer,[2] Dow and Harper[3]).

In a series of studies carried out by the author with collaborators, the life cycles of a large number of characteristic cardiac lesions occurring in rheumatic fever have been studied. These lesions are found in the left auricle,[34] valve rings,[31] valve leaflets,[32] intervalvular fibrosa,[31, 35] conduction system,[36] aortic and pulmonic roots,[37] myocardium,[38] blood vessels,[39] and pericardium.[40] It was shown that the majority of these lesions may heal with such complete restitution to integrity that it requires the closest scrutiny to reveal stigmas of their past occurrence. Nevertheless, these stigmas occur with remarkable consistency and are very widespread, even when healing has gone on to completion. Using these stigmas as evidences of past rheumatic disease, Sohval and Gross[35] have recently shown that calcific aortic valve sclerosis (Mönckeberg type) is a distinct pathological entity (sui generis) and can exist quite apart from an underlying rheumatic basis. This conclusion was based on the histological findings in a series of hearts presenting the Mönckeberg process in which it was seen that the lesion frequently exists without appreciable evidence of any of the rheumatic stigmas otherwise found in very high incidence in completely extinct but definite ancient rheumatic fever.

It seemed then quite logical to apply the same criteria to those human hearts which contained blood vessels in the valves but appeared otherwise normal. Since it was of prime importance to establish the possibility of the existence of blood vessels in such otherwise seemingly intact hearts, it appeared advisable to first carry out these studies in a highly selected group of specimens least subject to criticism as to whether or not the valves had been the seat of a mild inflammatory process. If it could be shown that such carefully selected specimens possess blood vessels in the absence of inflammatory stigmas, one could then enter into the statistical question on the incidence of blood vessels in normal valves. On the other hand, if it could be shown that there exists overwhelming evidence against the acceptance of vascularized human heart valves as normal, such statistical observations would be

of value only in that they indicate the existence of mild valvular lesions in perhaps an hitherto unsuspected proportion of the population.

Accordingly, 44 hearts were selected from the last 4,000 autopsies performed in the laboratories of the Mount Sinai Hospital. Among these 4,000 autopsies, 700 hearts were subjected to injection by the author's method.[28] It may be mentioned parenthetically that these injected specimens did not show as high an incidence of vasculature in the supposedly normal hearts as did the noninjected specimens. The reason for this will become clear in the discussion.

To recapitulate, these 44 specimens presented no evidence clinically and, by currently acceptable standards, no evidence grossly that the heart had been subject to previous inflammatory disturbance. Syphilis was carefully ruled out by the history and Wassermann test. In the light of the microscopic findings present in these specimens, it must be mentioned that a careful review of the gross material revealed inconspicuous macroscopic changes in the leaflets or chordae tendineae attachments (such as small isolated thickenings of the leaflet edges, minor straightening of the scalloped borders, occasional abrupt insertions of the chordae tendineae into the cusps, etc.) which in retrospect undoubtedly represent minimal gross abnormalities. These were, however, of so mild an extent and simulated so closely the wear and tear tension changes commonly found in these leaflets that they could not be interpreted as evidences of disease without corroboration of the microscopic findings.

These specimens were fixed in 10 per cent neutral formalin saline* and sectioned by the standardized technic of Gross, Antopol, and Sacks.[41] The sections were stained according to the methods previously described by Gross and Ehrlich.[38] In the microscopic examination of these hearts, particular attention was paid to the following seventeen sites, viz., endocardium, myocardium and pericardium of the left auricle, rings† and leaflets of the mitral (anterior and posterior), aortic, tricuspid and pulmonic valves, intravalvular fibrosa of the anterior mitral leaflet, roots of the aorta and pulmonary artery, and pericardium as a whole.

In order to compare the incidence of lesions in these sites with those possibly occurring in hearts from individuals who had no history indicating cardiac affection and whose valves were normal microscopically and possessed no blood vessels—in other words, normal control hearts—a series of 100 specimens were studied by the same methods and charted statistically under the seventeen sites mentioned above. In addition, there were also examined hearts from 13 cases

*Solution of formaldehyde, U. S. P., 10 parts; 1 per cent sodium chloride solution, 90 parts. This solution is rendered neutral with a weak alkali.

†For definitions of these sites see reference 1.

of grossly monovalvular extinct rheumatic disease, 50 human hearts injected by Wearn's technic,[18] 50 calf hearts similarly injected, 50 uninjected calf hearts, uninjected and injected swine, sheep, rabbit and guinea pig hearts, and serial sections from numerous human, ox, and swine embryos.

MICROSCOPIC FINDINGS IN 100 CONTROL HEARTS WITH NORMAL NONVASCULARIZED VALVES

Reference to Table I discloses the fact that lesions in the left auricle (endocardium, myocardium, and pericardium) were represented in these control specimens by reduplications of the endocardium in 20 per cent of the cases. These were delicate, flat and collagenous, invariably occurred in the older age periods (generally from the sixth decade on), and have already been described by the author[34] as probably representing a sclerotic proliferative process which can be generally differentiated from the reduplications found in rheumatic disease. In 15 per cent of the cases very mild scatterings of lymphocytes and occasional dilated capillaries were found in the pericardium of the left auricle. These mild infiltrations are undoubtedly attributable to the fact that in a number of these cases there were present inflammatory lesions of the lungs with, possibly, some continguity process to the pericardium. No inflammatory lesions were found in the left auricular myocardium, and, more significantly, in no instance were lesions found in two or three of these sites in the same left auricle.

It has already been shown by Gross and Kugel[1] that capillaries only were found in the valve rings of 100 normal hearts with the following frequency:

Anterior mitral valve ring	1%
Posterior mitral valve ring	2%
Aortic valve ring	0%
Tricuspid valve ring	14%
Pulmonary valve ring	7%

These capillaries are very delicate, generally circular on cross-section (except in the tricuspid ring where they frequently appear as large sinusoidal spaces), in no way resemble granulation tissue, and are not surrounded by inflammatory cells. The fibroelastic leaflets distal to these rings presented no vasculature whatsoever. This absence of blood vessels was confirmed in many instances by injection and by serial sections.

Of great importance is the fact that the valve leaflets showed no appreciable thickening or reduplication of the proximal layers (auricularis layer of the auriculoventricular valves and ventricularis layer of the semilunar valves) and, except in the oldest age periods, no evidence of absorption of the chordae tendineae. The closure line of the leaflets occasionally showed mild fibroelastic thickenings.

The intervalvular fibrosa was completely devoid of capillaries or inflammatory cells both in the main body of this structure (annulus extension) as well as in the boundary between the left auricular myocardial wedge and the annulus extension. Inasmuch as repeated reference will be made to this boundary, which extends from the region of the aortic ring to the tip of the left auricular myocardial wedge, this site will be termed "myocardial fibrous boundary of the intervalvular fibrosa."

It has already been shown by the author[37] that capillaries are occasionally present between the fibroelastic and muscular strands of the pulmonic root media in approximately 24 per cent of normal hearts. These capillaries are extremely inconspicuous, arise from the blood vessels in the adventitial layer, and rarely penetrate beyond the inner third of the media. Rare capillaries confined to the medial-adventitial zone were observed in 25 per cent of normal aortic roots. Scars were rare and inconspicuous.

In 10 per cent of these control hearts mild scatterings of lymphocytes were noted in the pericardium of several of the standardized blocks. As mentioned before, however, these lymphocytes showed no particular concentrations, nor were there present increased numbers of capillaries or other findings suggestive of a previous rheumatic pericardial lesion.[40]

Of great importance is the fact that of the seventeen sites under which these statistics were listed, lesions were never found in more than three of these sites in any of the hearts of the normal non-vascularized control series. In the vast majority of cases, only one lesion was present. This consisted either of a flat reduplication of the left auricular endocardium or of capillarization of one of the rings, chiefly the tricuspid.

MICROSCOPIC FINDINGS IN THIRTEEN HEARTS WITH GROSSLY MONOVALVULAR EXTINCT RHEUMATIC DISEASE

In contrast to the paucity of the above mentioned findings are the extraordinarily high incidence and consistent occurrence of stigmas in extinct rheumatic disease recognizable grossly and microscopically as such. The lesions present in these hearts have already been reported by Sohval and Gross[35] in their studies on aortic calcific sclerosis of the Mönckeberg type. The statistical data in this group, rather than in a group of extinct grossly polyvalvular rheumatic disease, have been selected to be presented in this report, inasmuch as it appears of value to compare the incidence of lesions in the 44 supposedly normal vascularized valve hearts with a series which could be considered definitely rheumatic in which, however, the gross lesions showed minimal deviation from the normal.

TABLE I

COMPARISON OF PERCENTAGE INCIDENCE OF MICROSCOPIC LESIONS IN THE HEARTS OF THE NORMAL NONVASCULARIZED VALVE SERIES, GROSSLY MONOVALVULAR EXTINCT RHEUMATIC SERIES, AND THE SUPPOSEDLY NORMAL VASCULARIZED VALVE SERIES

	LEFT AURICLE				ANTERIOR MITRAL VALVE		POSTERIOR MITRAL VALVE		AORTIC VALVE		TRICUSPID VALVE		PULMONIC VALVE		INTERVALVULAR FIBROSA		GREAT VESSEL ROOTS		PERICARDIUM
	ENDOCARDIUM	MYOCARDIUM	PERICARDIUM	2 OR MORE SITES	RING	LEAFLET	RING	LEAFLET	RING	LEAFLET	RING	LEAFLET	RING	LEAFLET	ANNULUS EXTENSION	MYOCARDIAL-FIBROUS BOUNDARY	PULMONIC	AORTIC	(SITES SEVERAL)
Normal nonvascularized valves (100 cases)	20	0	15	0	0	0	0	0	0	0	0	0	0	0	0	0	24	25	10
Grossly monovalvular extinct rheumatic disease (13 cases)	63	37	74	74	53	95	47	74	58	21	32	26	26	5	5	85	37	68	80
Supposedly normal vascularized valves (44 cases)	69	32	92	69	35	62	56	41	41	12	35	14	28	14	21	71	74	64	74
Supposedly normal vascularized valves with 4 Aschoff body cases eliminated (40 cases)	68	30	95	68	33	60	58	40	40	12	33	10	28	10	18	73	78	68	70
Supposedly normal vascularized valves with Aschoff bodies in myocardium (4 cases)	75	50	75	75	50	75	75	50	50	50	75	50	75	50	50	50	75	75	100

As will be seen from Table I, the lesions in this group were extraordinarily common and widespread in the seventeen sites referred to in this report. Particular attention should be directed to the incidence of lesions in the left auricle, in the various rings and valve leaflets, in the fibrous boundary of the intervalvular fibrosa, in the great vessel roots, as well as in several pericardial sites. It appears then from these findings that rheumatic fever leaves a very high incidence of inconspicuous but widespread stigmas in certain sites of the heart, even when the inflammatory process has become completely extinct and when the disease was, so far as one could discern, relatively mild.

MICROSCOPIC FINDINGS IN FORTY-FOUR SUPPOSEDLY NORMAL HEARTS POSSESSING BLOOD VESSELS IN THE VALVES

The not infrequent discovery of rheumatic lesions in hearts at the autopsy table, from patients in whom there is no history of rheumatic fever and in whom this disease has never been suspected during life, is well known to pathologists. Hawking[42] has recently reported that in addition to those in whom the condition was diagnosed clinically as rheumatic fever, 1.2 per cent of 1,380 necropsies on other patients dying at the Presbyterian Hospital revealed evidence of clinically unsuspected rheumatic heart disease. Careful search through the standardized sections of the 44 hearts comprising the group under discussion revealed the surprising fact that four of them presented myocardial Aschoff bodies (Fig. 1). Inasmuch as these hearts were carefully selected to rule out all clinical and gross anatomical evidence of abnormality, this observation becomes extremely important to the problem under discussion. First, it indicates that apart from the autopsy findings of "silent" rheumatic hearts, this disease may exist in an active state (Rothschild, Gross, and Kugel[43]) with, however, such subdued virulence that the only other suggestive evidence of its existence is the presence of blood vessels in the valves which otherwise appear to be grossly intact. Second, the incidence of rheumatic stigmas in these four hearts is not significantly different from the other supposedly normal hearts with vascularized valves so that, were it not for the discovery of the Aschoff bodies, they would properly fall into this group.

In order to avoid confusion of the issue, the incidence of the rheumatic stigmas in the seventeen selected sites are listed in Table I under the following headings: 44 cases with supposedly normal vascularized valves, four of which, however, revealed Aschoff bodies in the myocardium; 40 cases with supposedly normal vascularized valves in which the four cases with Aschoff bodies are eliminated; four cases with supposedly normal vascularized valves which revealed Aschoff bodies in the myocardium.

It will be noted that in the three subdivisions of this group, the incidence and distribution of lesions bear a striking similarity to those found in the extinct rheumatic cases. Of considerable importance and interest are the findings in the left auricle. As will be observed, lesions were found in the endocardium and myocardium and, particularly in

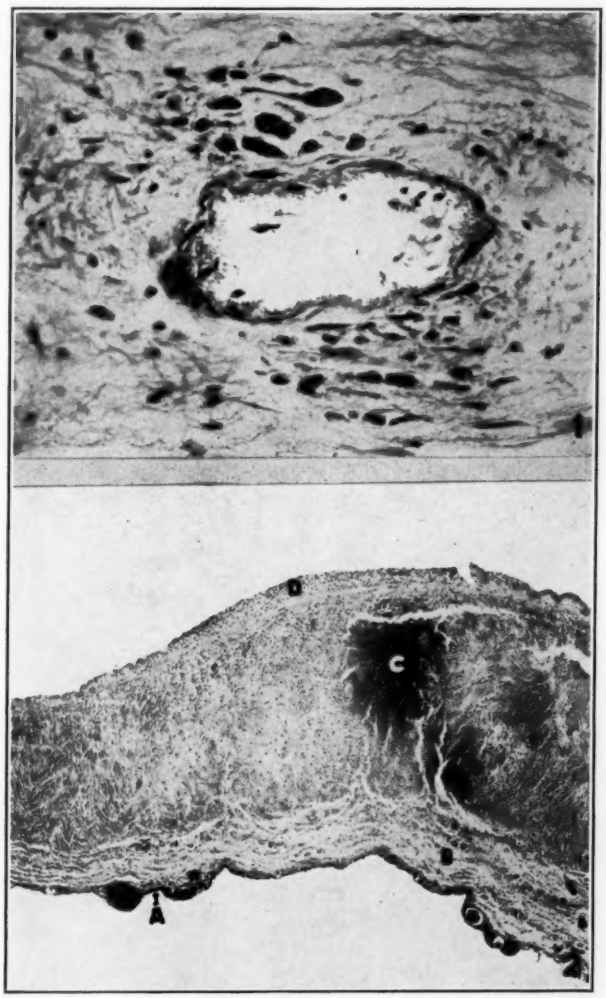

Fig. 1.—Case from supposedly normal vascularized valve series. Patient aged fifty-nine years. Hematoxylin and eosin stain. Medium power.

Typical Aschoff body in interventricular septum.

Fig. 2.—Case from supposedly normal vascularized valve series. Patient aged twenty-nine years. Hematoxylin and eosin stain. Medium power.

Cross-section through anterior mitral leaflet showing injected blood vessels situated within the auricularis layer. *A*, auricularis layer containing blood vessels surrounded by lymphocytes; *B*, spongiosa layer. Note several injected vessels near basal portion; *C*, fibrosa layer; *D*, ventricularis layer.

the pericardium, with a frequency considerably above that found in the control nonvascularized valve series, and, moreover, the incidence

of these lesions is approximately the same as that noted in the extinct monovalvular rheumatic series. Furthermore, in 69 per cent of this series lesions were found in two or more of the three auricular sites examined. This is in sharp contrast to the findings in the nonvascularized control series.

The incidence of capillaries together with scatterings of lymphocytes in the various valve rings again approach very closely that found in the extinct rheumatic series. This, therefore, is another distinct difference from the normal nonvascularized controls. In most instances, these capillaries were thicker than those occasionally found in normal rings. They were sometimes surrounded by scatterings of lymphocytes. Not infrequently, these lesions were distributed within scarred ring spongiosa and annulus.

The findings in the valve leaflets will be discussed in the following section. Suffice it to say here that many of the leaflets showed reduplications of the proximal layers and that blood vessels frequently occurred in these same layers and were generally surrounded by mild lymphocytic infiltration (Fig. 2).

During the first three or four decades of life, the normal myocardial-fibrous boundary of the intervalvular fibrosa consists of an inconspicuous connective tissue layer situated between the closely apposed left auricular myocardial wedge and the main collagenous annulus extension of the intervalvular fibrosa. Capillaries and inflammatory cells are not present either in the boundary or in the intervalvular fibrosa proper. In later age periods accumulations of fat tissue are deposited within this boundary zone. This tissue generally possesses delicate capillaries between the areolar septums. Of paramount interest was the observation that in 71 per cent of the hearts comprising the so-called normal vascularized valve series, a definite lesion existed within the myocardial fibrous boundary (Figs. 3, 4, 5) and in 21 per cent, within the annulus extension of the intervalvular fibrosa (Fig. 5). In the former the lesion consisted of a loose reticular tissue containing many stout and often distorted capillaries. Rare lymphocytes were occasionally present. These lesions could be easily differentiated from the normal fat accumulations. Moreover, they occurred with great regularity even in the earliest age periods. In the annulus extension of the intervalvular fibrosa, capillaries were observed penetrating for a variable distance toward the endocardium. These were occasionally surrounded by lymphocytes. These findings, therefore, by themselves sharply differentiate the so-called normal vascularized valve series from the normal nonvascularized controls.

Capillarization of the pulmonic root as well as lesions of the aortic root (capillaries and scars) occurred in very high incidence. Indeed, the incidence bore a striking resemblance to that found in the monovalvular extinct rheumatic series. In 74 per cent of the hearts several of

the standardized blocks from the same case showed pericardial lesions These consisted generally of scattered lymphocytes which often tended to concentrate in the neighborhood of the lamina propria layer (Fig. 6). Moreover, there was often a definite increase in the size and number of capillaries within the pericardium, and also a widening and thickening of the septums of the areolar tissue. These findings are in distinct

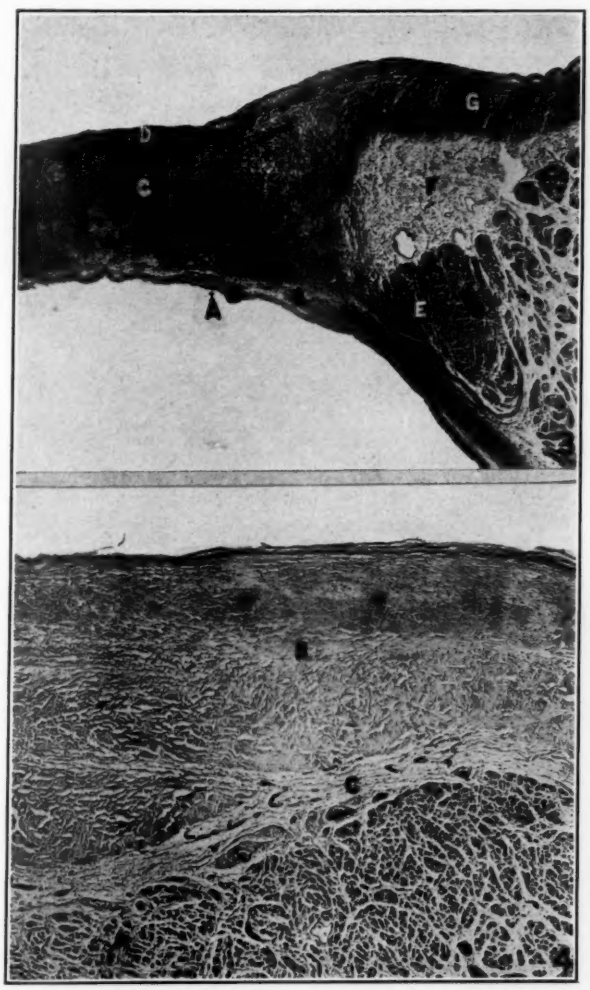

Fig. 3.—Case from supposedly normal vascularized valve series. Patient aged thirty-one years. Weigert's elastic and van Gieson's connective tissue stain. Low power.

Cross-section through basal portion of anterior mitral leaflet including left auricular myocardial wedge. *A*, auricularis layer containing an injected vessel; *B*, spongiosa layer; *C*, fibrosa layer; *D*, ventricularis layer; *E*, left auricular myocardial wedge; *F*, myocardial-fibrous boundary of intervalvular fibrosa containing numerous capillaries within a reticular framework; *G*, annulus extension of intervalvular fibrosa.

Fig. 4.—Case from supposedly normal vascularized valve series. Patient aged thirty-six years. Hematoxylin and eosin stain. Medium power.

Cross-section through annulus extension of intervalvular fibrosa including left auricular myocardial wedge. *A*, left auricular myocardial wedge; *B*, annulus extension of intervalvular fibrosa; *C*, myocardial-fibrous boundary of intervalvular fibrosa containing granulation tissue type vessels within a reticular framework.

contrast to the 10 per cent incidence of mild lymphocytic scatterings found in the normal nonvascularized valve control series.

Of greatest importance is the fact that every heart in this series showed lesions in at least six of the seventeen sites selected (not listed in Table I). The average heart showed lesions in ten or eleven sites, and several in sixteen or seventeen sites. A further significant differ-

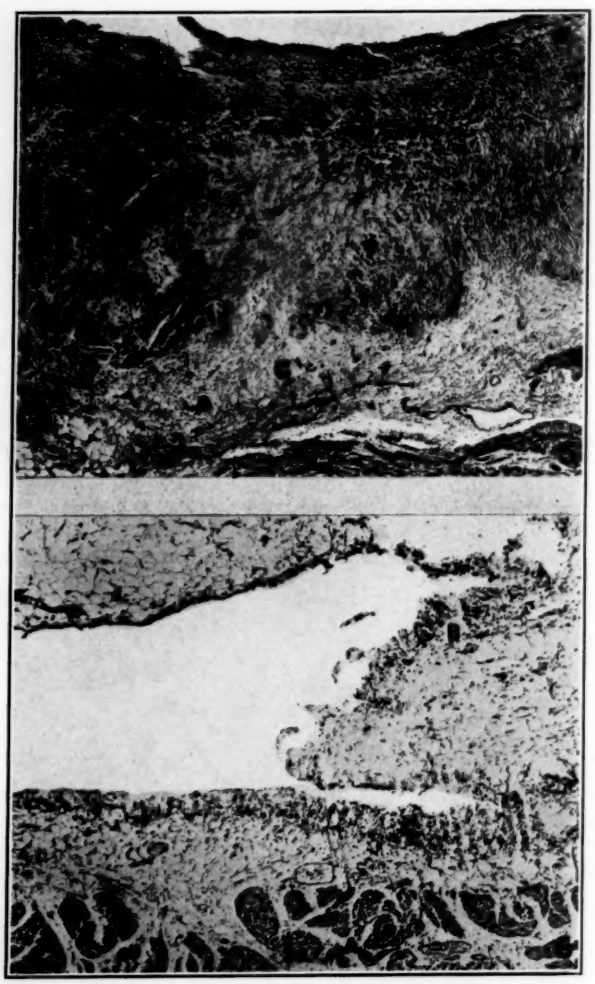

Fig. 5.—Case from supposedly normal vascularized valve series. Patient aged nineteen years. Hematoxylin and eosin stain. Medium power.

Cross-section through annulus extension of intervalvular fibrosa including left auricular myocardial wedge. *A*, left auricular myocardial wedge; *B*, annulus extension of intervalvular fibrosa. Note penetrating capillaries (injected) surrounded by scattered lymphocytes. *C*, myocardial-fibrous boundary of intervalvular fibrosa containing granulation tissue type vessels within a reticular framework. Note penetration of these capillaries into annulus extension.

Fig. 6.—Case from supposedly normal vascularized valve series. Patient aged twenty-seven years. Hematoxylin and eosin stain. Medium power.

Cross-section through pericardial portion of left auricle. *A*, left auricular myocardium; *B*, pericardium infiltrated with lymphocytes. Note concentration of lymphocytes around *C*, lamina propria.

ence from the normal nonvascularized valve control series was the frequent presence of delicate reduplications of the proximal valve layers and the occasional early absorption of chordae tendineae insertions.[32]

It is obvious, therefore, that this series differs markedly from the normal nonvascularized controls in the high incidence of inflammatory stigmas; in their wide distribution; in the association of reduplications on the proximal valve layers, however mild; in the high incidence of ring capillarization; and in the almost invariable presence of stigmas in the left auricle, myocardial fibrous boundary of the intervalvular fibrosa, great vessel roots, and pericardium. The significance of these findings will be taken up in the discussion.

MICROSCOPIC FINDINGS IN FIFTY HUMAN HEARTS AND IN THE HEARTS OF SEVERAL SPECIES OF ANIMALS INJECTED BY WEARN'S TECHNIC

The following pertinent facts concerning the histological structure of the calf's heart should be borne in mind: the spongiosa of the auriculoventricular valves generally contains large quantities of fat tissue; both the ring and the spongiosa layer contain capillaries, arterioles, and arteries which extend for a variable distance toward the free edge of the leaflets; occasional vessels are present within the arterialis layer of these leaflets and capillaries may sometimes be seen within the ventricularis mantle of the intervalvular fibrosa; the collagenous layer (annulus extension) of the latter, however, rarely contains vessels; the aortic ring invariably contains numerous vessels confined to an extraordinarily large ring spongiosa; these vessels generally do not ascend for any appreciable distance toward the free edge of the aortic leaflets—when they do so, however, they lie within the spongiosa layer; reduplications of the proximal valve layers and inflammatory cells are not found in the normal calf's heart. In contrast to this, the blood vessels within the valve leaflets of the supposedly normal human heart valves generally lie within the proximal layers of the valve leaflets and are not infrequently surrounded by scatterings of lymphocytes.

Blood vessels could be seen macroscopically as well as microscopically within the valve leaflets of the uninjected calf hearts. These vessels were also seen in the injected specimens. Furthermore, it was observed that, when the injection technic was varied, this did not appreciably influence the incidence of successful injections. Thus, for example, when the pressure was dropped to as low as 80 mm. of mercury, successful injections were obtained. It is possible, however, that in these specimens there was less complete filling of the vascular network. Similar observations were made on a number of swine and sheep hearts. On the other hand, neither macroscopic nor microscopic studies of injected and uninjected rabbit or guinea pig hearts disclosed

capillaries within the fibroelastic portions of the leaflet, irrespective of the technic employed. It becomes obvious, therefore, that, if blood vessels are present in valve leaflets, no unusual injection technic appears to be necessary for their successful demonstration. Furthermore, however successful the injection technic may be, the results rarely equal the findings as disclosed by microscopic observation. For, even in the

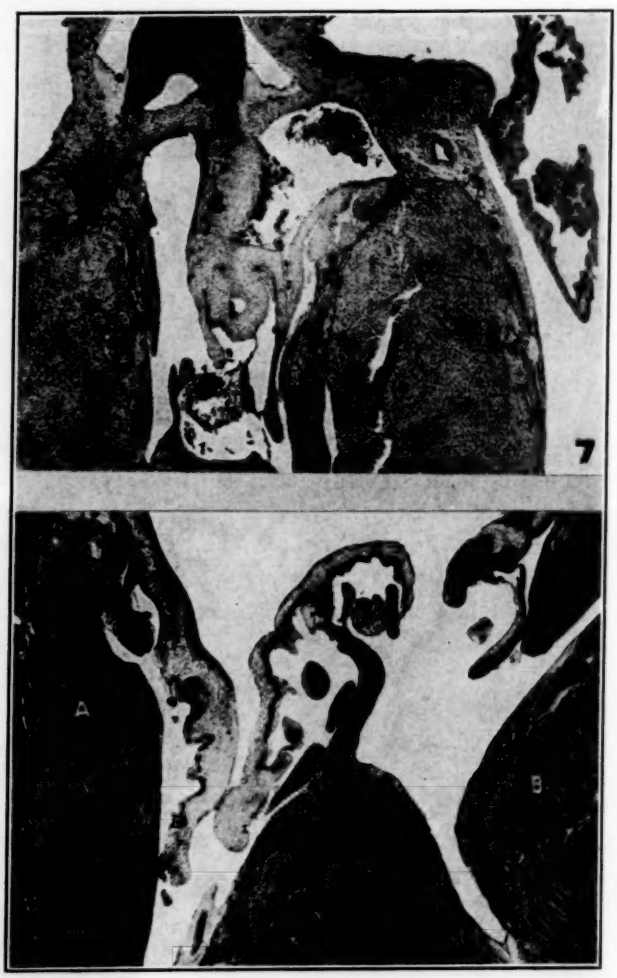

Fig. 7.—Frontal section through 11 cm. (crown-rump) human embryo. Hematoxylin and eosin stain. Medium power.
A, interventricular septum; *B*, wall of left ventricle; *C*, anterior mitral leaflet. Note spongy structure and absence of blood vessels. *D*, left auricle.

Fig. 8.—Frontal section through 30 cm. (crown-rump) ox embryo. Hematoxylin and eosin stain. Medium power.
A, Interventricular septum; *B*, wall of left ventricle; *C*, anterior mitral leaflet. Note spongy structure containing numerous capillaries.

most successful injection, the injection mass does not penetrate every capillary within the valve leaflet or myocardium, whereas microscopic examination invariably reveals these uninjected vessels.

The results of injecting the human hearts were similar to the findings mentioned above. Thus, of the fifty hearts injected by this method, only four showed gross vascularization of the anterior mitral leaflet. All four hearts, however, had gross alterations of the valves, which, though not advanced, were nevertheless suggestive of a healed rheumatic process. This was confirmed by subsequent examination of the above mentioned seventeen cardiac sites. Incidentally, this examination revealed ring capillaries (normal) in several of the hearts, not disclosed by the injection technic. It seems, therefore, that, whenever the heart valves possessed blood vessels, they could be invariably demonstrated microscopically, and while a successful injection afforded a more spectacular display of the vessels, these methods in no way increased the incidence of the discovery of blood vessels; on the contrary, the incidence of valve vasculature as determined by microscopic study was greater than that disclosed by the injection technic.

MICROSCOPIC FINDINGS IN HUMAN EMBRYOS AND IN EMBRYOS OF SEVERAL ANIMAL SPECIES

Examination of serial sections from a large number of human embryos ranging from 4 mm. upward, kindly placed at the author's disposal by Professor George Streeter, of the Carnegie Institute of Embryology, as well as 20 human embryos serially sectioned in these laboratories, failed to disclose myocardium in the primitive valve cushions of the human embryo (Fig. 7). These consist of embryonal myxomatous tissue which is clearly delimited from the spongy myocardium. In the auriculoventricular valves, the apex of the auricular myocardial wedge not infrequently enters the base of the valve structure, but the limits of the portion destined to be the fibroelastic structure are sharp and distinct. Of greatest importance is the fact that, whereas careful search through these serial sections failed to disclose blood vessels within the valve cushions, blood vessels were readily demonstrated within the valve leaflets of ox and swine embryos (Fig. 8).

DISCUSSION

From the findings reported above, it is seen that even when the selection of the so-called normal human vascularized valve series was so carefully made that only 44 out of 4,000 specimens were used for the examination, these specimens showed a very dramatic difference from the normal nonvascularized ones. The latter were conspicuous for the paucity of stigmas in any way resembling those found in the vascularized series. On the other hand, in the so-called normal vascularized valve group, stigmas of previous inflammatory disease were consistently found and bore a more than casual resemblance to those observed in the extinct rheumatic control series. Moreover, in every instance a

number of stigmas were found together in the same heart. The chief sites as noted were the left auricle, the myocardial-fibrous boundary of the intervalvular fibrosa, great vessel roots, and the pericardium. The rather wide distribution of these sites suggests strongly that the lesions found therein were not related anatomically to the vascularization of the valves but bore a common genetic relationship to it. In other words, the same agent produced both the lesions in the various sites mentioned, as well as the vascularization of the valves.

To put it succinctly, these hearts differed completely from normal ones possessing no vessels within their valves. Moreover, statistically as well as anatomically the differences bore a striking resemblance to the findings in a definite rheumatic series. Of great interest is the fact that in four of these cases (9 per cent), Aschoff bodies were found after careful examination of many sites, yet these latter cases did not differ essentially from the so-called normal vascularized series in which no Aschoff bodies were found. As mentioned previously, were it not for the discovery of the Aschoff bodies, these four cases properly belonged in the supposedly normal vascularized valve series. These facts, therefore, together with the close resemblance in the quantity and distribution of the stigmas as well as the presence of delicate reduplications of the proximal layers of the valves, afford the strongest support to the view that the supposedly normal vascularized valve series owes the presence of blood vessels in the valves to a previous mild and, in most instances, completely healed rheumatic process. That activity may still persist in such cases, however, is shown by the finding of Aschoff bodies in 9 per cent of this group of cases. In further support of this contention is the fact that there exists a completely smooth graded series of specimens described by the author with collaborators[31, 32, 34, 36-40] in which the findings range from those demonstrated in indisputable rheumatic hearts (with Aschoff bodies and other typical macroscopic and microscopic lesions) to those described as occurring in this supposedly normal vascularized valve series. Moreover, the findings in the various groups merge imperceptibly from one group into the other.

If it be assumed that another inflammatory disease or diseases may be responsible for the eventual production of these lesions, one should find in an appreciable number of autopsies the acute stages of some hitherto unknown cardiac or other disease which might conceivably produce the same stigmas. Experience with a large material has demonstrated that to all intents and purposes this does not exist. The relatively rare diseases which also implicate the valves, such, for example, as syphilis, tuberculosis, and Libman-Sachs' disease, are associated with characteristic clinical and pathological findings and, moreover, occur statistically in so low a frequency that it is inconceivable that these could be responsible for more than an insignificant propor-

tion of valve vascularization. The conclusion, therefore, is inescapable —that either vascularization does not exist in normal valves leaflets or, if does exist, it must be extraordinarily rare.

In a report by Ritter, Gross, and Kugel[30] dealing with this subject, several possibilities were suggested to account for the existence of blood vessels occasionally found in supposedly normal hearts. Three questions were asked which it seems can now be answered quite definitely. The first one was whether it is possible that these valves had really been the seat of an endocarditis, that granulation tissue blood vessels had in this way been produced, and that all signs of inflammation in the valve had disappeared without leaving appreciable changes other than blood vessels. The answer to this is largely in the affirmative. It must be noted, however, that with more recent knowledge on the rather inconspicuous stigmas or telltale marks of ancient inflammation, appreciable traces are left in these hearts and can be found on careful microscopic examination. In this connection, one should employ the term "tension changes" with considerable reserve. When these take the form of definite reduplications and are associated with thickening of the smooth muscle of the valve leaflets, a careful search should be made for the stigmas referred to above.

The second question asked by Ritter, Gross, and Kugel was whether it is possible that even though many of the blood vessels found in these valves are distinctly of the arterial and venous type, they may have arisen none the less as granulation tissue vessels. The answer to this is also in the affirmative. In recent reports by Gross and Friedberg,[31, 32] it has been shown that, in rheumatic fever, muscular wall arterial vessels can be stimulated to formation in great numbers at various sites within the endocardium of valve leaflets (subaortic angle, arterialis layer, etc.) in which they are otherwise not normally present. Furthermore, during the active phases of rheumatic fever, various stages in the development of these vessels may be found.

The third question asked by the above mentioned authors was whether serial sections might have disclosed evidence of inflammatory lesions in those instances in which single section failed to disclose them. As already mentioned, the newer data on the end-results of inflammatory lesions furnish a means of discerning evidences of past inflammation even without serial sections. It cannot be denied, however, that before a valve can be considered normal, serial sections must be made.

The existence of vascularized valves normally in a number of species of animals has been a stumbling block to many of the investigators in this field, for it is a great temptation to assume that the blood vessels sometimes found in human heart valves are analogous to the former. That this is not the case, however, is clearly shown by the above mentioned findings. When vessels are present in a given species, they can

be found with the greatest ease, they occur consistently, they are not associated with any inflammatory stigmas and they can be found invariably on microscopic examination. On the other hand, injection technic does not demonstrate valve vascularization in those species in which this does not normally occur.

It has already been shown that animals normally possessing vascularized valves also show vessels in sections of the embryo heart valves. The human embryo, however, possesses neither myocardium nor blood vessels in the valves. It appears, therefore, that Langer's contention is no longer tenable and this observation removes any logical basis for the origin of such vessels in normal human heart valves.

There remains, therefore, to discuss the reason for the discrepancies between the findings herein recorded and those reported by other recent observers, particularly by Wearn and his coworkers. It is the contention of the latter authors that with improvement in injection technic, they were able to obtain an increasing incidence in vascularization of human heart valves until it reached 74 per cent. Nevertheless, they point out that in twelve valves from a series of eighty-eight supposedly normal hearts they were able to demonstrate blood vessels microscopically when injection failed to do so. This observation is similar to the one made by the present author in 1921[28] and is confirmed by the studies herein presented. In this connection, it is of interest to note that although the author's injection technic[28] was found superior to that employed by Wearn, apparently no injection technic thus far devised can as faithfully portray the incidence of vascularization or capillarization as can the microscope, particularly if serial sections are used. It appears, therefore, that one must search for another source for the vasculature demonstrated by Wearn and his coworkers.

It has been shown above that human heart valves which possess blood vessels in the fibroelastic portions are not normal. However, to assume that 74 per cent (Wearn's figures*) of hearts coming to autopsy could have been the seat of an inflammatory lesion of the valves is untenable. Although Wearn states that the most common distribution of vessels in the mitral leaflet is an extension of from 3 mm. to 7 mm. into the free leaflet and that in 40 per cent of the vascularized tricuspid valves the vessels extended to about one-half the distance to the free edge, it is suggested that in the majority of his cases (i.e., those not the seat of inflammatory stigmas) this extension below the base possibly represents a macroscopic appraisal of the injection and that a microscopic examination of this material would reveal that these vessels lie in the apex of the auricular myocardial wedges. In estimating the extent of these wedges, it must be borne in mind that

*Since this article was submitted, Wearn and his associates (AM. HEART J. 13: 7, 1937) reported that only 13 per cent of the auriculoventricular valves examined by them would be accepted by Gross and Kugel as being truly vascularized.

sclerotic changes not infrequently produce scarring to such an extent that the limits are not sharp. However, a careful examination of a van Gieson stained preparation will generally reveal isolated myocardial bundles from which the original extent of the wedge may be reconstructed. It is further suggested that the semilunar valves, which displayed vasculature in considerably lower incidence, either belonged to diseased hearts of the type herein described under the group of so-called normal hearts with vascularized valves, or possessed vessels confined to the ring region. A low incidence of vessels in the latter site is apparently normal.

Inasmuch as the thesis with which this report concerns itself deals with the existence of blood vessels situated within the fibroelastic portions of the valve leaflets as defined by Gross and Kugel[1] and employed in these studies, it does not appear to be of any further interest to describe the course of blood vessels which occur in myocardium or such portions of the root of the valve as still possess some extension of the auricular myocardial wedge. The original stimulus to investigate this problem has been to verify or deny Köster's claim[44] that the existence of blood vessels in normal valve leaflets affords an anatomical basis for the assumption that endocarditis is of embolic origin. Although such embolic origin is undoubtedly true, at least in some instances of the bacterial endocarditides, in the light of these studies it cannot serve as an explanation for the origin of rheumatic valvulitis. Furthermore, even if the vessels were conceded to extend for a short distance into the base of the valve, this would certainly not account for the formation of verrucae at the closure line, a considerable distance beyond the base of the valve.

Wearn and his collaborators have shown that according to their figures the incidence of valvulitis does not correspond to the incidence of vascularization of the valves. Thus, valve vascularization was noted by them in the following order of frequency: mitral, tricuspid, pulmonic, aortic. They, therefore, do not link up the incidence of vascularization with that of endocarditis. These findings, however, do not correspond to the observations made in these laboratories. In previous reports, Gross and Friedberg[31, 32] have demonstrated an extraordinarily high incidence of vascularization of the valves in rheumatic fever, this occurring almost invariably in the mitral, aortic and tricuspid valves and somewhat less frequently in the pulmonic. Moreover, approximately the same incidence of vascularization is found in the rings, even when vessels fail to extend into the fibroelastic portion of the leaflet distal to the ring. Thus, the existence of valvulitis parallels the presence of blood vessels provided the ring is considered part of the valve leaflet. As has been shown, however, overwhelming evidence at present available points to the fact that these blood vessels are secondary to the inflammation.

SUMMARY

There have been described in this report the findings in 100 non-vascularized normal human valves, 44 human hearts in which the valves were vascularized but appeared grossly normal, 13 hearts from extinct monovalvular rheumatic disease, 50 human hearts, 50 calf hearts, and a number of rabbit and guinea pig hearts injected by Wearn's technic, as well as a number of uninjected calf, swine, rabbit and guinea pig hearts, and swine, ox and human embryos serially sectioned. It is shown that the so-called normal vascularized human hearts present widespread stigmas which in incidence and distribution bear striking resemblance to the findings in undisputed, extinct rheumatic specimens. Reasons are given which indicate very strongly that rheumatic fever, which has gone on to complete healing, is responsible for the formation of these blood vessels. It is further shown that rheumatic fever can produce muscular vessels as one of the results of granulation tissue evolution. A description is given of the normally vascularized calf heart valves, and attention is drawn to the differences between these valves and their blood vessels, and those sometimes found in human hearts. It is further shown that while ox and swine embryos display blood vessels in their valves, these are not found in the heart valves of human embryos. As a consequence, there exists no rational embryogenetic basis on which to explain the occurrence of blood vessels found in human hearts.

A discussion of injection technic together with new observations reinforces the belief that such technic affords no information to the problem under discussion which cannot be better obtained by microscopic observations on serial sections. The conclusion is drawn that blood vessels do not exist in normal valves or, if they do, they must be very rare.

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STUDIES IN CARDIOVASCULAR SYPHILIS

I. Teleroentgenography in the Diagnosis of Early Syphilitic Aortitis: A Comparison of Findings in 1,000 Syphilitic and 600 Nonsyphilitic Individuals*

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CURRENT interest in the diagnosis of cardiovascular syphilis centers in the effort to recognize early syphilitic aortitis uncomplicated by aortic insufficiency or saccular aneurysm. The prevention of these later and usually fatal complications depends in part on the adequacy of treatment of early syphilis, but much more largely, considering the relatively small number of recently infected persons who receive such adequate treatment, on the recognition of the aortic lesion before it has produced irreparable anatomical damage.

The failure to recognize early aortitis in the living patient is due in part to the often silent course of the lesion and in part to confusion arising from the fact that the symptoms and clinical signs which it produces may be closely duplicated by two common nonsyphilitic conditions—essential hypertension and arteriosclerosis. The great discrepancy which exists between the clinical and autopsy diagnosis of early syphilitic aortic disease has been pointed out by Moore, Danglade, and Reisinger,[1] who found that only 4, or 3.8 per cent, of 105 cases of syphilitic aortitis proved at autopsy had been diagnosed during life.

With added clinical experience, however, many observers have acquired increasing confidence in their ability to diagnose early aortitis correctly in a high proportion of cases. By the expedient of clinical restudy of living patients, Moore and Metildi,[2] for example, have shown that 19.1 per cent of 115 patients diagnosed as uncomplicated aortitis subsequently developed indubitable and graver forms of cardiovascular syphilis, thereby establishing the validity of the earlier and more difficult diagnosis. In an additional 35.6 per cent, there was presumptive evidence that the original diagnosis was correct. These workers feel, therefore, that in certain instances, the diagnosis of aortitis may be safely made even in the presence of essential hypertension and arteriosclerosis, or both. They list seven diagnostic criteria for uncomplicated syphilitic aortitis as follows: "(1) Teleradiographic and fluoroscopic evidence of aortic dilatation; (2) increased retromanubrial dullness; (3) a history of circulatory embarrassment; (4) a tympanitic bell-like, tambour accentuation of the aortic second

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sound; (5) progressive cardiac failure; (6) substernal pain, and (7) paroxysmal dyspnea." They insist that to justify the diagnosis of uncomplicated aortitis, at least three of the above criteria must be present in a patient with known late syphilis but without mitral disease. Their point of view has not yet met with general acceptance.

Since aortic dilatation is a prominent feature of syphilitic aortitis at autopsy, it is not surprising that many roentgenological studies have been carried out in the effort to aid in its early diagnosis. As a result of these studies, most workers in this field are agreed that in syphilitic aortitis there is usually diffuse dilatation and loss of elasticity of the aorta, increased density of the root and sometimes of the knob, and, in particular, localized dilatation and excessive pulsation of the first portion of the ascending aorta (Steel,[3] Sproull,[4] Brown,[5] Kurtz and Eyster,[6] and Hampton, Bland, and Sprague[7]). Opinions concerning the value of roentgenological studies in the diagnosis of uncomplicated syphilitic aortitis are conflicting. However, a few observers, particularly Maynard and his associates,[8] believe that in certain instances the diagnosis of simple aortitis may be made by teleroentgenogram even in the absence of symptoms or clinical signs. Most roentgenologists feel that in order to obtain an accurate estimate of the aortic shadow, fluoroscopy must be combined with one of the more exact methods of accurate measurements of the outline of the heart and great vessels: orthodiagraphy, kymography, or teleroentgenography.

PROBLEM

Since teleroentgenography is the method most commonly used for mensuration of the aortic shadow, this study was undertaken to determine as accurately as possible its value in the diagnosis of early uncomplicated syphilitic aortitis. Having available data on a large number of unselected syphilitic and nonsyphilitic individuals with identical cardiac examinations, including teleroentgenographic studies, it occurred to us that a comparison of the two groups might provide a more accurate answer than previous studies of smaller groups of patients.

Material Studied

The material of this study is compiled from the records of patients admitted to the Public Health Institute during the past thirteen years. Prior to its reorganization in 1931, cardiovascular examinations, including a complete medical history and physical examination, at least two blood pressure observations, a teleroentgenogram, and an electrocardiogram, were required of the majority of patients whether or not they had venereal disease. While these procedures are evidently unnecessary except in patients with syphilis, and have since been discontinued, the material gathered in the application of this routine has

made available for analysis and comparison a large amount of information about both syphilitic and nonsyphilitic individuals of analogous age, sex, and occupational groups.*

The method of study in all patients was as follows: About 2,500 x-ray films of nonsyphilitic and syphilitic persons were examined. Of these, nearly a thousand were discarded because of technical imperfections in the roentgenogram: i.e., films blurred, not centered properly, stained by chemical deterioration, or unmeasurable as to aortic width because of other mediastinal shadows. When the roentgenogram was sufficiently satisfactory to permit accurate measurements of the Vaquez-Bordet[9] aortic arch width and of the size of the heart, the patient's history was withdrawn from the files and analyzed for the pertinent factors of race, sex, age, the presence or absence of nonsyphilitic heart disease, including the presence or absence of peripheral arteriosclerosis, blood pressure, cardiac, and Vaquez-Bordet aortic arch measurements, the presence or absence of syphilitic infection, the duration of syphilis when known, the type and amount of antisyphilitic treatment received by the patient before coming to this clinic or before the cardiac examination was made, the presence or absence of syphilitic heart disease, the results of fluoroscopic examination, and the presence of signs or symptoms of uncomplicated syphilitic aortitis. These data were transferred to punch cards through the courtesy of Dr. Herman N. Bundesen, Commissioner of Health of Chicago, and were subjected to statistical analysis. It is felt that the manner in which this material was selected guarantees against possible artificial selection and precludes the question of the unconscious selection of material by reference from a syphilis to a cardiac clinic. There were available 600 records of nonsyphilitic individuals and 1,000 of persons with syphilis.

The absence of syphilis in the group of 600 nonsyphilitic persons was determined by the absence of a history of infection and of symptoms or physical signs attributable to syphilis, and by the presence of a negative serological test in each member of the series. The existence of syphilis in the 1,000 syphilitic patients was established in every instance by indisputable anamnestic, clinical, or laboratory evidence. All stages of syphilitic infection are represented from the chancre to general paresis.

RESULTS

A summary and comparison of the syphilitic and nonsyphilitic material by age groups and by the presence or absence of cardiovascular abnormalities is presented in Tables I and II.† A tabulation by sex

*We wish to express our thanks to Dr. Joseph Earle Moore for his advice and help in the compilation of these data and to Miss Usilton, of the U. S. Public Health Service, for the preparation of the scatter charts published herewith.

†In the compilation of these data it was realized that the Vaquez-Bordet method of measuring the width of the supracardiac shadow is not a true estimate of the diameter of the aorta. It was adopted, however, because it is the method most commonly used in interpreting teleroentgenographic studies of the cardiovascular stripe.

is omitted, since the group of females is small and since there were no striking differences between the sexes. The 600 nonsyphilitic persons included 478 males and 122 females; the 1,000 syphilitic patients, 749 males and 251 females. An analysis by race is also omitted since of the 600 nonsyphilitics 96.5 per cent were white, and only 3.5 per cent were colored; and of the 1,000 syphilitics 92.6 per cent were white, and 7.4 per cent were colored. The age groups selected are 0 to 19 years, and thence by decades until the age of 50 years, after which all decades are grouped together because of the small number of patients available in each of the separate later decades. As shown in Table I, 29.8 per cent of the 600 nonsyphilitic individuals had some

TABLE I

NONSYPHILITIC PATIENTS ACCORDING TO AGE GROUPS AND TYPE OF CARDIOVASCULAR ABNORMALITY

AGE	TOTAL CASES	NO CARDIOVASCULAR ABNORMALITY	TOTAL WITH SOME FORM OF CARDIOVASCULAR ABNORMALITY	TYPE OF CARDIOVASCULAR ABNORMALITY			
				RHEUMATIC HEART DISEASE	THYROID HEART DISEASE	ESSENTIAL HYPERTENSION	ARTERIOSCLEROSIS WITH AND WITHOUT HYPERTENSION
0-19	17	14	3 (11.7%)	2	-	1	-
20-29	225	208	17 (7.5%)	11	2	4	-
30-39	135	112	23 (17.0%)	10	1	6	6
40-49	111	68	43 (38.7%)	5	-	4	34
50+	112	19	93 (83.0%)	3	-	1	89
Total	600	421	179 (29.8%)	31	3	16	129

demonstrable abnormality of the cardiovascular apparatus. This was practically the same as the incidence of nonsyphilitic heart disease (30.6 per cent) occurring either alone or in combination with syphilitic heart disease among the 1,000 syphilitic patients (Table II). In both

TABLE II

SYPHILITIC PATIENTS CLASSIFIED ACCORDING TO AGE GROUPS AND TYPE OF CARDIOVASCULAR ABNORMALITY

AGE	TOTAL CASES	NO CARDIOVASCULAR ABNORMALITY	NO. WITH UNCOMPLICATED CARDIOVASCULAR SYPHILIS	NO. WITH NONSYPHILITIC CARDIOV. ABNOR.			TYPE OF NONSYPHILITIC CARDIOVAS. ABNORMALITY			
				AND SYPHILITIC CARDIOVASCULAR DISEASE	WITHOUT SYPHILITIC CARDIOVASCULAR DISEASE	TOTAL	RHEUMATIC HEART DISEASE	THYROID HEART DISEASE	ESSENTIAL HYPERTENSION	ARTERIOSCLEROSIS WITH AND WITHOUT HYPERTENSION
0-19	10	8	1	-	1	1	-	-	1	-
20-29	184	161	2	-	21	21	10	1	10	-
30-39	304	263	10	1	30	31	10	-	13	8
40-49	272	131	33	10	98	108	7	-	34	67
50+	230	58	27	43	102	145	3	-	3	139
Total	1000	621	73	54	252	306	30	1	61	214

groups of individuals and in both sexes, the incidence of some form of nonsyphilitic cardiovascular abnormality rises steadily with each decade and is apparently due to the rising incidence of hypertension and arteriosclerosis.

The patients with cardiovascular syphilis have been divided into four groups, based on the usually accepted standards of diagnosis: i.e., (1) aortic insufficiency occurring in the absence of a history of rheumatic fever and uncomplicated by mitral disease; (2) saccular aneurysm, in this series always of the thoracic aorta; (3) aortic insufficiency and aneurysm occurring together; and (4) simple or uncomplicated syphilitic aortitis. In all instances the last diagnosis was

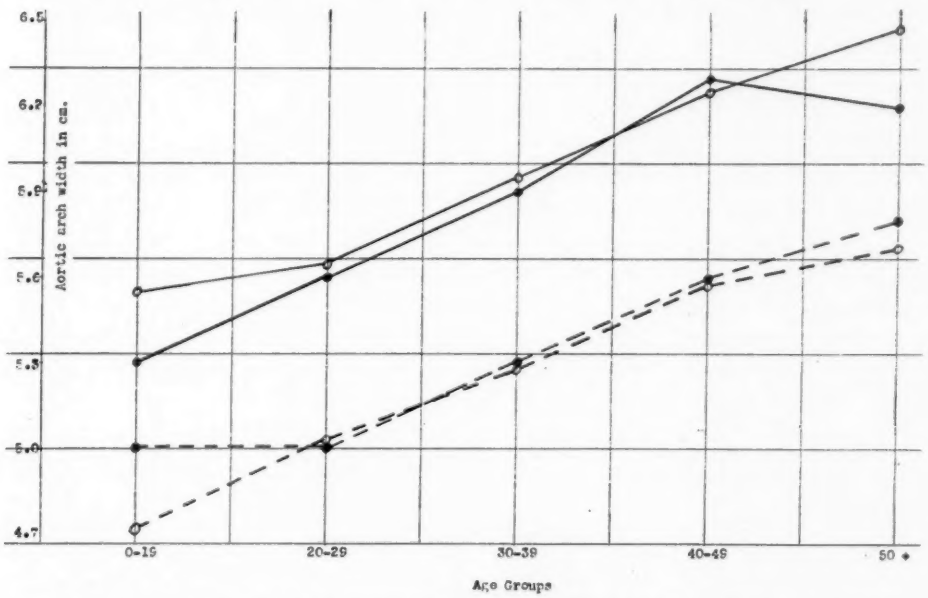

Fig. 1.— .—. Nonsyphilitic males without heart disease of any type; .---. nonsyphilitic females without heart disease of any type; o—o syphilitic males, excluding nonsyphilitic heart disease and cardiovascular syphilis; o---o syphilitic females, excluding nonsyphilitic heart disease and cardiovascular syphilis.

made on the basis of the presence of at least three of the criteria suggested by Moore and Metildi,[2] and in none does the diagnosis rest on roentgenological evidence alone. These results are shown in Table III. As is to be expected, the incidence of cardiovascular syphilis in any form, and particularly in the more serious forms, increases with advancing age.

The relationship of age to aortic dilatation demonstrable by teleroentgenogram has been approached in two ways. In Fig. 1 is shown the arithmetical average of the Vaquez-Bordet measurement by sex and age groups for (1) all nonsyphilitic patients with no evidence of cardiovascular abnormality of any type and (2) all syphilitic patients,

TABLE III

TYPE OF SYPHILITIC HEART DISEASE ENCOUNTERED IN 1,000 SYPHILITIC PERSONS

AGE GROUPS	TOTAL CASES	SYPHILITIC HEART DISEASE—COMPLICATED OR UNCOMPLICATED	TYPE OF SYPHILITIC HEART DISEASE—COMPLICATED AND UNCOMPLICATED			
			AORTITIS	AORTIC INSUFFICIENCY	ANEURYSM	AORTIC INSUFFICIENCY AND ANEURYSM
0-19	10	1 (10.0%)	1	–	–	–
20-29	184	2 (1.0%)	2	–	–	–
30-39	304	11 (3.6%)	8	3	–	–
40-49	272	43 (15.8%)	22	7	8	6
50+	230	70 (30.4%)	9	10	39	12
Total	1000	127 (12.7%)	42	20	47	18

excluding those with both nonsyphilitic and syphilitic heart disease but including those in whom the only evidence of aortitis was an increase in the width of the aortic arch shadow. Considering, therefore, only those nonsyphilitic and syphilitic patients with clinically normal cardiovascular systems, there is no apparent tendency of syphilis per se to produce aortic dilatation over and above the degree to be expected with the passage of years.

Since averages do not correctly represent the entire story, the maximal and minimal aortic arch widths observed are presented by age and sex in Table IV. Both in nonsyphilitic and syphilitic patients with no clinical evidence of any form of heart disease, the maximum aortic arch width observed was 7.6 cm. in males (age group 40 to 49

TABLE IV

EXTREME VARIATIONS OF AORTIC ARCH WIDTH IN NONSYPHILITIC AND SYPHILITIC PATIENTS OF VARIOUS AGE GROUPS WITH AND WITHOUT HEART DISEASE (NONSYPHILITIC IN ROMAN TYPE, SYPHILITIC IN ITALICS)

SEX	AGE GROUP	EXTREME VARIATIONS OF AORTIC ARCH WIDTH, CM.		
		NO HEART DISEASE	HEART DISEASE NONSYPHILITIC	SYPHILITIC HEART DISEASE COMPLICATED OR UNCOMP.
M	0-19	4.7 - 5.8	5.5 - 5.5	–
		4.1 - 6.2	*5.4 - 5.4*	–
	20-29	4.1 - 7.3	5.2 - 7.2	–
		4.5 - 7.5	*4.8 - 6.3*	*5.7 - 7.5*
	30-39	4.5 - 7.0	6.2 - 7.6	–
		4.5 - 7.1	*5.5 - 7.2*	*6.0 - 8.6*
	40-49	5.2 - 7.6	6.3 - 9.8	–
		4.8 - 7.6	*5.3 - 7.9*	*5.5 - 13.0*
	50+	5.5 - 6.8	6.2 - 9.7	–
		5.2 - 7.0	*5.3 - 9.4*	*5.5 - 13.0*
F	0-19	4.2 - 5.8	4.5 - 5.0	–
		4.7 - 5.1	– –	–
	20-29	4.2 - 5.9	4.4 - 4.5	–
		3.9 - 6.0	*3.9 - 7.6*	–
	30-39	3.9 - 7.0	5.0 - 8.0	–
		4.3 - 6.6	*5.0 - 6.9*	*6.2 - 7.5*
	40-49	5.2 - 6.4	5.6 - 7.5	–
		4.8 - 6.6	*5.6 - 7.9*	*5.9 - 8.3*
	50+	5.5 - 6.1	5.8 - 8.0	–
		5.2 - 6.2	*6.0 - 7.1*	*6.0 - 8.8*

years), and 7 cm. in females (age group 30 to 39 years). In both sexes, however, in patients over the age of 50 years, and in the presence of nonsyphilitic heart disease (usually hypertension plus arteriosclerosis), the maximum width for males was 9.7 cm. and for females 8.0 cm. These measurements are far in excess of those of many individuals with outspoken cardiovascular syphilis. The extreme limits of 13 cm. in patients with syphilitic heart disease are, of course, accounted for by saccular aneurysms.

In order to give a somewhat clearer comparison of a nonsyphilitic with a syphilitic population, a scatter chart has been prepared (Fig. 2), showing the distribution of all nonsyphilitic patients with and without cardiovascular abnormalities by age groups compared with aortic arch width, and a regression or trend line is indicated. The

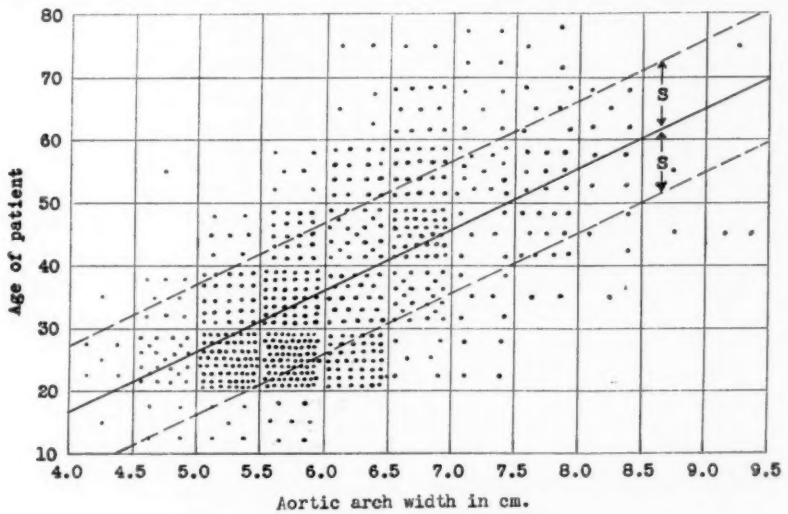

Fig. 2.—Six hundred nonsyphilitic patients.

"S" area is the standard error of estimate, showing how nearly the estimated values agree with the values actually observed. In this figure the area included between the two broken lines contains approximately 71 per cent* of all observed values. In this group the standard error of estimate is quite high, and the trend line permits an estimate of the aortic width of a patient of a given age group only within ten years. For example, the regression line shows that patients 50 years of age have an average aortic arch width of 7.5 cm., but the same value can be expected in patients aged 40 to 60 years.

Figure 3† shows regression lines based on the coefficient of correlation between age and aortic arch width in three groups of patients:

*$\frac{100 \times Sy}{Oy}$

†Thanks are due Dr. Paul D. Rosahn for his aid in the statistical interpretation of these data.

(1) 600 nonsyphilitics; (2) 915 syphilitic patients, excluding those with aortic insufficiency and saccular aneurysm, but including those with uncomplicated aortitis; (3) 85 syphilitic patients with advanced cardiovascular syphilis, aortic insufficiency and aneurysm. The coefficients of correlation between age and aortic width for these three groups were as follows:

$$(1)\ r = +0.6281 \pm 0.0247;\ r^2 = 0.39$$
$$(2)\ r = +0.5897 \pm 0.0216;\ r^2 = 0.35$$
$$(3)\ r = +0.3205 \pm 0.0997;\ r^2 = 0.10$$

In each case the correlation coefficient is more than two and a half times its standard error, and they are all, therefore, statistically significant. The appended value of r^2, which is termed the coefficient of determination, shows what percentage of the variation in the depend-

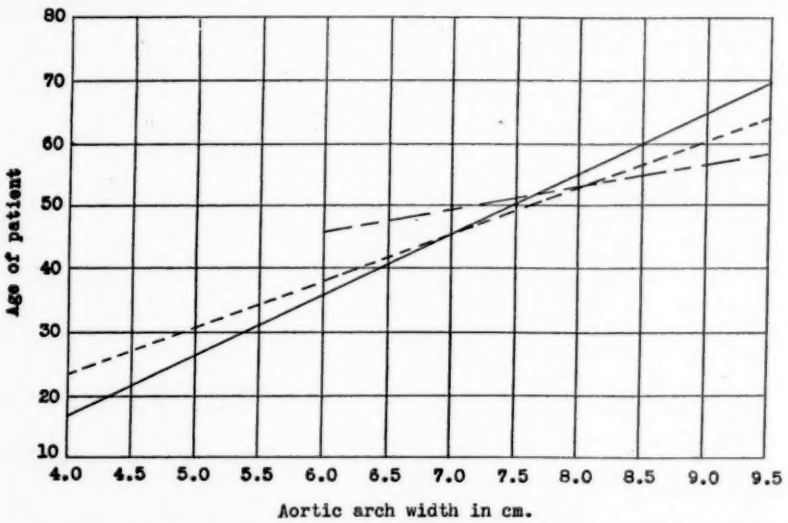

Fig. 3.—Comparison of aortic arch widths in centimeters in syphilitic and nonsyphilitic individuals according to age of patient.

—— Nonsyphilitic patients (600 cases); ---- syphilitic patients (excluding aortic insufficiency and saccular aneurysm, but including uncomplicated aortitis) (915 cases); — — — patients with cardiovascular syphilis (excepting uncomplicated aortitis) (85 cases).

ent variable is explained by the independent variable. In the nonsyphilitic group only 39 per cent of the increasing aortic arch width was due to increasing age, the rest having been caused by other factors such as arteriosclerosis, hypertension, etc. Similarly, in the syphilitic patients without syphilitic heart disease, except uncomplicated aortitis, only 35 per cent of the increasing aortic arch width with increasing age can be explained by the increasing age of the patient. In the 85 cases of aortic regurgitation and aneurysm, however, only 10 per cent of the widening of the arch shadow is due to the increasing age of the patient, the remaining 90 per cent being presumably due to syphilis plus the other factors operative in nonsyphilitic persons.

In Table V is shown in somewhat simplified form the incidence of aortic dilatation in nonsyphilitic patients as affected by the existence of various forms of nonsyphilitic cardiovascular abnormalities. The aortic widths are here classified in three categories, corresponding with the classification used by Maynard, i.e., normal, aortic arch widths up to 6.7 cm. in males, and to 6.2 cm. in females; borderline dilatation, from 6.7 cm. to 7.0 cm. in males, and from 6.2 cm. to 6.5 cm. in females; and definite aortic dilatation, 7.1 cm. or more in males, and 6.6 cm. or more in females. According to this classification, borderline or definite aortic dilatation occurs in 7.4 per cent of normal individuals. Rheumatic heart disease and hypertension alone account for an unexpectedly small increase in aortic width in this series of cases. Arteriosclerosis, with and without hypertension, is obviously the factor which produces aortic dilatation in nonsyphilitic patients in the majority of instances.

TABLE V

COMPARISON OF AORTIC ARCH WIDTHS (MAYNARD'S CLASSIFICATION) IN 600 NONSYPHILITIC INDIVIDUALS ACCORDING TO PRESENCE OR ABSENCE AND TYPE OF NONSYPHILITIC HEART DISEASE

AORTIC WIDTH	PER CENT OF PATIENTS WITH*				
	NO HEART DISEASE	RHEUMATIC HEART DISEASE	HYPERTENSION	ARTERIOSCLEROSIS	ARTERIOSCLEROSIS AND HYPERTENSION
Normal†	92.4	78.6	75.0	18.6	36.6
Borderline‡	5.4	7.1	6.2	16.2	12.6
Dilated§	2.0	14.2	18.7	65.1	50.7

*Omitting 3 patients with thyroid heart disease.
†Males, aortic width up to 6.7 cm.; females, aortic width up to 6.2 cm.
‡Males, aortic width from 6.8 to 7.0 cm.; females, aortic width 6.3 to 6.5 cm.
§Males, aortic width 7.1 cm. or over; females, aortic width 6.6 cm. or over.

TABLE VI

COMPARISON OF AORTIC ARCH WIDTHS (MAYNARD'S CLASSIFICATION) IN 1,000 SYPHILITIC INDIVIDUALS WITH AND WITHOUT HEART DISEASE

AORTIC WIDTH	NO HEART DISEASE	SYPHILITIC AORTITIS, COMPLICATED AND UNCOMP.	AORTIC INSUFFICIENCY AND ANEURYSM, COMPLICATED AND UNCOMPLICATED	NONSYPHILITIC HEART DISEASE ONLY*			
				RHEUMATIC	ESSENTIAL HYPERTENSION	ARTERIOSCLEROSIS	ARTERIOSCLEROSIS AND HYPERTENSION
	PER CENT	PER CENT	PER CENT	PER CENT	PER CENT	PER CENT	PER CENT
Normal†	92.1	22.5	3.7	83.3	89.2	51.4	49.2
Borderline‡	2.9	17.8	3.7	12.5	5.4	21.6	18.0
Dilated§	5.0	59.7	92.6	4.2	5.4	27.0	32.8

*Omitting one patient with thyroid heart disease.
†Males, aortic width up to 6.7 cm.; females, aortic width up to 6.2 cm.
‡Males, aortic width from 6.8 to 7.0 cm.; females, aortic width 6.3 to 6.5 cm.
§Males, aortic width 7.1 cm. or over; females, aortic width 6.6 cm. or over.

A similar classification of the syphilitic patients is provided in Table VI. As shown by this table, borderline and definite aortic dilatation occurred with the same frequency (7.9 per cent) in the 593 syphilitic individuals without demonstrable heart disease of any type as in the 422 nonsyphilitics without heart disease (7.2 per cent). The inclusion among the group of syphilitics without heart disease of patients with aortic dilatation but no other evidence of early aortitis, adds to the significance of this observation. It is of interest to note also that 22.5 per cent of the patients with aortitis had no teleroentgenographic evidence of aortic widening and that unquestionable aortic dilatation was present in only 59.7 per cent of the group.

SUMMARY AND CONCLUSIONS

In an attempt to evaluate aortic mensuration by teleroentgenography in the diagnosis of uncomplicated early syphilitic aortitis, we have compared 1,000 unselected syphilitics with 600 unselected nonsyphilitic individuals of the same occupational, sex, and age groups. The Vaquez-Bordet measurement of the supracardiac shadow was used in comparing the width of the aortic arch. In every instance the presence or absence of syphilis was established without question, and all patients were subjected to identical cardiovascular studies. A compilation of these data showed that:

1. The incidence of cardiovascular syphilis among the group of 1,000 syphilitic patients was essentially the same as that noted by others who had also studied large groups of patients.

2. The increased widening of the supracardiac shadow resulting from essential hypertension and arteriosclerosis with or without hypertension was the same in nonsyphilitic as in syphilitic individuals without syphilitic heart disease.

3. The increase in the width of the aortic arch shadow as a result of advancing age was the same in both syphilitic and nonsyphilitic individuals without heart disease.

4. Only 59 per cent of the patients with clinically recognizable syphilitic aortitis showed teleroentgenographic evidence of aortic dilatation.

5. There is no evidence that the diagnosis of uncomplicated syphilitic aortitis can be made by teleroentgenography alone. Fluoroscopy and careful clinical evaluation of symptoms and physical signs are essential.

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THE ELECTROCARDIOGRAM IN HYPERTENSION WITH ESPECIAL REFERENCE TO LEAD IV*

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INTRODUCTION

THE conception of the significance of the electrocardiogram in cases of hypertension has been influenced by the efforts to make a special use of electrocardiography in studying the condition of the heart muscle and the coronary arteries. Although of theoretical interest, its knowledge at first seemed to be of little or no clinical importance; however others, as well as we, have lately gathered adequate evidence to the contrary. Experiments as well as clinical observations proved means to increase the knowledge concerning the myocardium in the different forms of hypertension. Nevertheless, important problems remained unsolved. Using thoracic leads as a routine method† combined with the standard leads, it appears to us that we have gained fresh insight into the origin and also into the cause of absence of a number of characteristic changes in the electrocardiogram.

In a total of 2,000 curves, we found 228 cases of hypertension with which we tried to answer the following questions:

1. To what degree do hypertension and left axis deviation coincide? What is the cause of absence of left axis deviation in cases of distinct hypertension?

2. What is the significance of the negative T-wave in Lead I and of the positive T-wave in Lead III in cases of left axis deviation?

3. Are the convexity of the S-T line in Lead I and the concavity of the S-T line in Lead III in electrocardiograms with left axis deviation of any clinical interest?

4. What are the electrocardiographic differences between the curves found in cases of pronounced left axis deviation and those brought about by coronary thrombosis or those occurring in bundle or bundle-branch block?

5. Is it justifiable to attach clinical importance to the occurrence of an S-wave in Lead IV followed by an extreme convexity of the S-T line?

I. HYPERTENSION AND LEFT AXIS DEVIATION

A. Data.—Hypertension and so-called left axis deviation (R_1 being higher than 12 mm. and S_3 lower than –5 mm.) do not always coincide; neither is the height of the blood pressure directly proportional to the

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†For technical details see Nederl. Tijdschr. v. Geneesk. 80: 225, 1936.

degree of left axis deviation. Although in cases of a pronounced increase of the systolic blood pressure R_1 is usually found higher and S_3 lower than normal, exceptions are not rare. Conversely, left axis deviation is found sometimes in cases of normal systolic blood pressure; for instance, in aortic valve defects and mitral insufficiency, and in one case, in spite of hypertension, we found right axis deviation in mitral stenosis (S_1 low in regard to R_1 and R_1 low and R_3 too high in regard to R_2 and R_1). Among 100 patients with a systolic blood pressure over 150 mm. Ziskin[1] found only 44 cases of left axis deviation, Nuzum and Elliot[2] found 60 per cent; and other investigators[3] also have drawn attention to the frequent absence of left axis deviation in cases of hypertension. According to Ziskin[1] moreover, left axis deviation occurs less often when the blood pressure is over 200 mm. mercury than when the tension is from 150 to 200 mm. These figures apply to standard leads only. When the changes in the thoracic leads are taken into consideration, altogether different figures are obtained. In the thoracic lead as we record it (right arm electrode in fourth left intercostal space near the sternum—left leg electrode) the R-wave never exceeds +17 mm. (1 mm. volt corresponding to 1 cm. string deviation), and Q is never under −2 mm. In the thoracic lead left axis deviation manifests itself by an increase in height of the R-wave and a decrease in depth, and sometimes disappearance, of the Q-wave. The relation R:Q, normally averaging about 2 and showing extremes of 8 and about 1, now amounts to 10 and more. Cases of coronary thrombosis with anterior infarction in which the so-called C_2-type occurs[4] and curves resulting from bundle-branch or arborization block should be excluded.

In 228 cases of hypertension we found:

Left axis deviation in standard leads only	20 per cent
Left axis deviation in standard and thoracic leads	44 per cent
Left axis deviation in thoracic leads only	19 per cent
Left axis deviation completely absent	17 per cent

In other words, 64 per cent showed left axis deviation in standard leads, a result which very nearly approaches that of Nuzum and Elliot; the thoracic lead being used in addition, a left axis deviation was found in 83 per cent of the cases. Ziskin is of the opinion that the frequency of left axis deviation decreases with tensions over 200 mm. We found a frequency as given in Table I. The frequency of the left axis devia-

TABLE I

SYST. BL. PRESS., LEFT AXIS DEV.	IN I-IV*	IN I-III	IN IV ONLY	ABSENT
150-200 mm. (94 cases)	38%	20%	20%	22%
200-250 mm. (75 cases)	47%	12%	21%	20%

*Lead IV, thoracic lead (fourth left intercostal space—left leg electrode).

tion, manifesting itself in standard leads only, decreases slightly with an increase in tension; on the other hand, the left axis deviation occurring in all leads increases, thereby causing a slight increase in the total left axis deviation in cases with a tension of over 200 mm. mercury.

We have studied this same relation for the diastolic blood pressure and have arranged the results in Table II. The increase in left axis

TABLE II

DIAST. BL. PRESS., LEFT AXIS DEV.	IN I-IV	IN I-III	IN IV ONLY	ABSENT
0-100 mm. (96 cases)	40%	31%	16%	13%
100-150 mm. (116 cases)	41%	13%	24%	22%

deviation recorded in Lead IV is smaller than its decrease in the standard leads, thus resulting in a decrease of nearly 10 per cent of the total left axis deviation when the diastolic blood pressure exceeds 100 mm. mercury.

Our figures for the pulse pressure are as given in Table III. This shows that the left axis deviation is influenced little or not at all by the pulse pressure.

TABLE III

PULSE PRESSURE, LEFT AXIS DEV.	IN I-IV	IN I-III	IN IV ONLY	ABSENT
25- 75 mm. (98 cases)	43%	23%	18%	16%
75-125 mm. (121 cases)	41%	21%	19%	19%

In summary, we have found that left axis deviation does not occur much more often when the systolic blood pressure is 200-250 mm. than when it is 150-200 mm. but that its frequency certainly does not decrease either. In case the diastolic blood pressure increases, the left axis deviation decreases, in standard leads, but at the same time it increases in the thoracic leads, resulting in a slight decrease of the total left axis deviation when the diastolic blood pressure exceeds 100 mm. Hg. The amount of pulse pressure has little or no influence on the frequency or the degree of left axis deviation, no distinct connection being found between the amount of blood pressure and left axis deviation. We considered the possibility of a relationship between left axis deviation and dilatation of the heart. As in most cases an x-ray picture had been taken (at a distance of 2 m.); we were able to determine the heart measurements. We used the measure Dl + Dr according to Dietlen and Moritz,[5] because the results of more accurate methods, while more exact (Danzer's cardiothoracic ratio,[6] the prediction figures of Hodges and Eyster[7]) and other methods[8] are not more reliable.

The best results seem to be obtained by examining the heart *in vivo* before the screen and the x-ray picture before the light box. We determined the distance from a vertical line through the center of the

sternum to the left vertical tangent of the heart (Dl) and found the incidence as given in Table IV. The above figures show that, generally speaking, the left axis deviation increases distinctly with the dilatation of the left ventricle; only in Lead IV did the occurrence of left axis deviation decrease distinctly. So far as our figures allow any conclusion, it seems remarkable that the frequency of left axis deviation decreases slightly at a dilatation of Dl = 10.5 – 12.5 cm. (especially in the arteriosclerotic hypertension group). In determining the total width of the heart, the relation is found as given in Table V. Here, too, we

TABLE IV

LEFT AXIS DEVIATION	IN I-IV	IN I-III	IN IV ONLY	ABSENT
Dl up to 9.5 cm. (62 cases)	31%	14%	23%	32%
Dl 9.5-10.5 cm. (54 cases)	60%	13%	15%	12%
Dl 10.5-12.5 cm. (65 cases)	43%	23%	12%	22%
Dl 12.5-15.5 cm. (26 cases)	69%	20%	7%	4%

find that an increase in heart size shows a marked increase in left axis deviation and a decrease of the occurrence of left axis deviation in Lead IV only. Furthermore, left axis deviation appeared to occur more frequently in old age than in middle age. Whether this is a physiological phenomenon, as Schlomka[9] supposes, we do not know. In our cases, however, we found that the groups of older patients as a rule had markedly dilated hearts when the electrocardiogram showed left axis

TABLE V

LEFT AXIS DEVIATION	IN I-IV	IN I-III	IN IV ONLY	ABSENT
Dl + Dr up to 12 cm. (14 cases)	43%	14%	14%	29%
12-14 cm. (66 cases)	38%	20%	23%	19%
14-16 cm. (58 cases)	48%	27%	13%	12%
16 cm. and up (37 cases)	65%	22%	3%	10%

TABLE VI

AGE	DL + DR	UP TO 12 CM.	12-14 CM.	14-16 CM.	16 CM. AND UP
0-50	(78 cases)	15%	33%	32%	52%
50-60	(65 cases)	9%	30%	43%	62%
60-70	(47 cases)	2%	40%	29%	58%

deviation. Therefore, in our opinion the increased frequency of left axis deviation in old age is caused, at least in part, by an increase in dilatation of the heart.

Regarding the cause of hypertension, it can be said that especially defects of the aortic valves are accompanied by left axis deviation; in those cases a marked dilatation of the left ventricle exists. The same applies to hypertension in mitral insufficiency. Also in chronic nephritis left axis deviation is usually found, but here too, in our cases, the heart

usually showed a pronounced increase in width. In arteriosclerotic hypertension left axis deviation occurs less frequently than, for example, in aortic insufficiency, but then the heart dilatation usually was not very marked.

To summarize, we found:

1. Eighty-three per cent of the cases of hypertension show left axis deviation when Lead IV is used also.

2. The left axis deviation shows itself more clearly in cases of higher systolic and diastolic tension but does not increase in frequency.

3. When the systolic blood pressure exceeds 200 mm. and the diastolic blood pressure 100 mm.Hg, left axis deviation (in standard leads only) decreases in frequency (in accordance with the figures of Ziskin); while in thoracic leads it increases in frequency. In the first case the total percentage of left axis deviation increases slightly; in the second it decreases distinctly.

4. There is a general relationship between left axis deviation and dilatation of the heart as Dl + Dr exceeds 14 cm., the left axis deviation increases distinctly in frequency. However, there are certain exceptions to this rule (see "Interpretation"). A higher degree of dilatation shows a decrease in the *exclusive* occurrence of left axis deviation in the thoracic leads, while in thoracic and standard leads evidence of the left axis deviation increases.

5. Hypertension in old age usually shows a more pronounced left axis deviation; in our cases, however, the heart was also more dilated.

6. Defects of the aortic valve and chronic nephritis especially are associated with left axis deviation, more so than arteriosclerotic hypertension. However, in our cases the first mentioned diseases coincided with higher degrees of heart dilatation than did the arteriosclerotic.

In our opinion the principal causes of the occurrence of left axis deviation in the electrocardiogram in hypertension are a clockwise rotation of the heart in its longitudinal axis and a dilatation of the left ventricle.

B. Interpretation.—Einthoven himself noticed the left axis deviation in hypertension[10]; Lewis,[11] among others, later confirmed this observation. However, both investigators saw cases of distinct hypertension in which left axis deviation was absent and realized that not only the problem of the origin, but also of the cause of the absence of left axis deviation, had to be solved. Lewis based his explanation on two assumptions: the first, that the normal electrocardiogram is a bicardiogram, composed of dextro- and levogram; the second, that the degree of deviation of the electrocardiogram is proportional to the quantity of muscle in action. Hypertrophy and dilatation of the left half of the heart will cause this to dominate and result in a left axis deviation (Lewis' "left preponderance"). When the right half of the heart shows hypertrophy (and dilatation) a "right preponderance" as a rule will be the result.

When, however, not only the left but also the right ventricle hypertrophies, the resulting relation of the muscles may be such that, for instance, in case of hypertension, not only an absence of preponderance but even a "right preponderance" may be the result. As yet neither of these assumptions of Lewis has been proved. We are still in doubt as to whether or not the electrocardiogram really is a bigram; the second assumption obviously cannot possibly be right: the electrocardiogram of children usually shows a much larger voltage than that of adults and in large animals it is often smaller than in human beings.

Herrmann and Wilson[12] and Burger[13] could therefore not share this opinion. Determining the exact weight of left and right ventricles Herrmann and Wilson found left axis deviation only at differences in weight of over 250 gm. Burger proved that normal, sometimes considerable, variations in the height of R- and S-waves are not proportional to differences in weight between the ventricles or of the ventricles separately. Another theory sees the cause of preponderance curves in a shifting of the anatomical or of the electrical heart axis (the sum total of all action currents generated in the systole). A dilatation usually implies a change in the position of the heart. Conversely, the form of the electrocardiogram is influenced by a shifting of the heart's position in respect to the electrodes, as Einthoven, Fahr and de Waart[14] and, more extensively, Cohn[15] were able to prove. Finally, by changing the position of the electrodes in regard to the heart (for instance, by applying the right arm electrode to the left arm, the left arm electrode to the left leg, etc.) a left axis deviation or a right axis deviation can be produced at will. One may rightly object that a shifting of the position of the heart to a degree as required in the experiments of Cohn, is never seen in hypertension. Moreover, this is accompanied by a change of position of P and T in the same direction as R, while in hypertension curves the T-wave is often found opposite to the main deviation of the ventricular complex.

Even if one believes an altered position of the heart by a rotation in its sagittal axis to influence the form of the electrocardiogram, this influence cannot possibly be very great. Boden and Neukirch[16] and later Burger[17] are of the opinion that hypertrophy curves are caused by a rotation of the heart in its longitudinal axis. Normally the right ventricle lies more in the frontal plane (the plane of the standard leads), the left ventricle more in the sagittal plane. According to Burger, this is why in normal cases the right ventricle has a larger electric effect than the left. Hypertrophy of the left ventricle causes the heart to rotate clockwise on its longitudinal axis, bringing the left ventricle more in the frontal plane. However, the degree of shifting is not necessarily proportional to the change in relation between the mass of muscle of the right and left ventricles.

Nuzum and Elliot[18] attribute the preponderance curves to coronary changes. They have come to this conclusion finding the left axis deviation far from constant in hypertension and often absent when the heart is markedly dilated; moreover they found left axis deviation to occur more frequently in angina pectoris without hypertension than in hypertension without angina pectoris. They suppose the left axis deviation to be brought about by intraventricular conduction disturbances caused by an insufficient blood supply of the conduction system and the myocardium resulting from coronary changes.

This conclusion is highly disputable. In the first place, the ventricular complex in hypertension hardly ever shows an increase in width, as it does as a rule in cases of intraventricular conduction disturbances. Besides, it does not seem justifiable to attribute left axis deviation of the electrocardiogram, as may be found in young people (e. q., with chronic nephritis), always to coronary changes. And finally the figures these authors give do not cover our data.* Ziskin,[1] who found left axis deviation in only 44 per cent of his cases, was of the opinion that as yet it seemed impossible to discover its cause or to estimate its significance.

The investigators, mentioned above, always took as a starting point the percentage of left axis deviation existing in hypertension and found

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PLATE A

I. Left Axis Deviation in All Leads

Fig. 1.—Man, aged forty-nine years, mitral insufficiency. Dyspnea on exertion, palpitation. Heart diameter 13.7 cm. Electrocardiogram: low P-waves in all leads. S_3, relatively low, corresponding small Q_3 (–1 mm.), and high R_4 (20 mm). S-T runs in the isoelectric level (normally aniso-electric). T_4, shallow, slightly diphasic. Conclusion: left axis deviation in all leads, T_4 indicates a not too favorable condition of the myocardium.

Fig. 2.—Woman, aged sixty-seven years, hypertension (220/115). Cardiac failure (dyspnea, edema, nocturia, palpitation). Heart diameter, 13.5 cm. Electrocardiogram: in Lead I low, diphasic T-waves, R_1, 14 mm. In Lead II: deep S-waves. A-V conduction time 0.20 sec. Lead III: deep S-waves (–23 mm.), T positive. Lead IV: relatively small Q-Wave, S-T isoelectric. Conclusion: left axis deviation in all leads. T_1 corresponding with cardiac failure.

II. Left Axis Deviation in Lead IV Only

Fig. 3.—Woman, aged forty-one years, palpitation, pain in chest and back on exertion, dyspnea. Tension, 120/85. Diameter of the heart, 13.5 cm. Electrocardiogram: Lead I no deviations. In Lead II S-T interval is somewhat anisoelectric. No S-wave. Lead III: Pardee-Q, negative T. Lead IV: diphasic P, shallow Q and high R summit (23 mm.). Conclusion: coronary sclerosis, beginning left dilatation; Pardee-Q masks left axis deviation in Lead III.

Fig. 4.—Man, tension 200/120. In Lead I a notch at the bottom of RS, prolongated S-T segment (0.36 sec.), high T-wave. Lead II: low T-wave. Lead III: *W*-shaped complexes, flat T-waves. Lead IV: small Q, high R, broad, blunt T-wave, Conclusion: *W*-shaped complexes, probably caused by coronary sclerosis, are masking left axis deviation in the standard leads; however, it is manifest in the chest lead.

Fig. 5.—Woman, aged forty-seven years, hypertension (200/90). Vague anginal complaints, palpitation, slight dyspnea on exertion, headaches. Heart of normal width (11.4 cm.). Urine normal. Electrocardiogram: in Lead I, no deviation. Lead II: high T-wave. Lead III: S perhaps a little too deep. Lead IV: pronounced left axis deviation (small Q-wave, high R-wave), T shallow. Conclusion: the elevated blood pressure has not as yet caused a marked dilatation of the heart. However, Lead IV shows already a left axis deviation; very probably the dilatation is already manifest in an anteroposterior plane.

Fig. 6.—Woman, aged forty-eight years, angina pectoris, hypertension (255/110). Heart slightly enlarged (14.5 cm.). Electrocardiogram: in Lead I no deviation. Lead II: low T-waves. Lead III: S-T takes off a little too high, is of convex shape, and proceeds into a negative T-wave. Left axis deviation is manifesting itself in Lead IV: shallow Q, high R-wave. The shallow T_4, negative T_3, and low T_2 point to a less favorable condition of the myocardium.

*We will revert to this subject in a following paper.

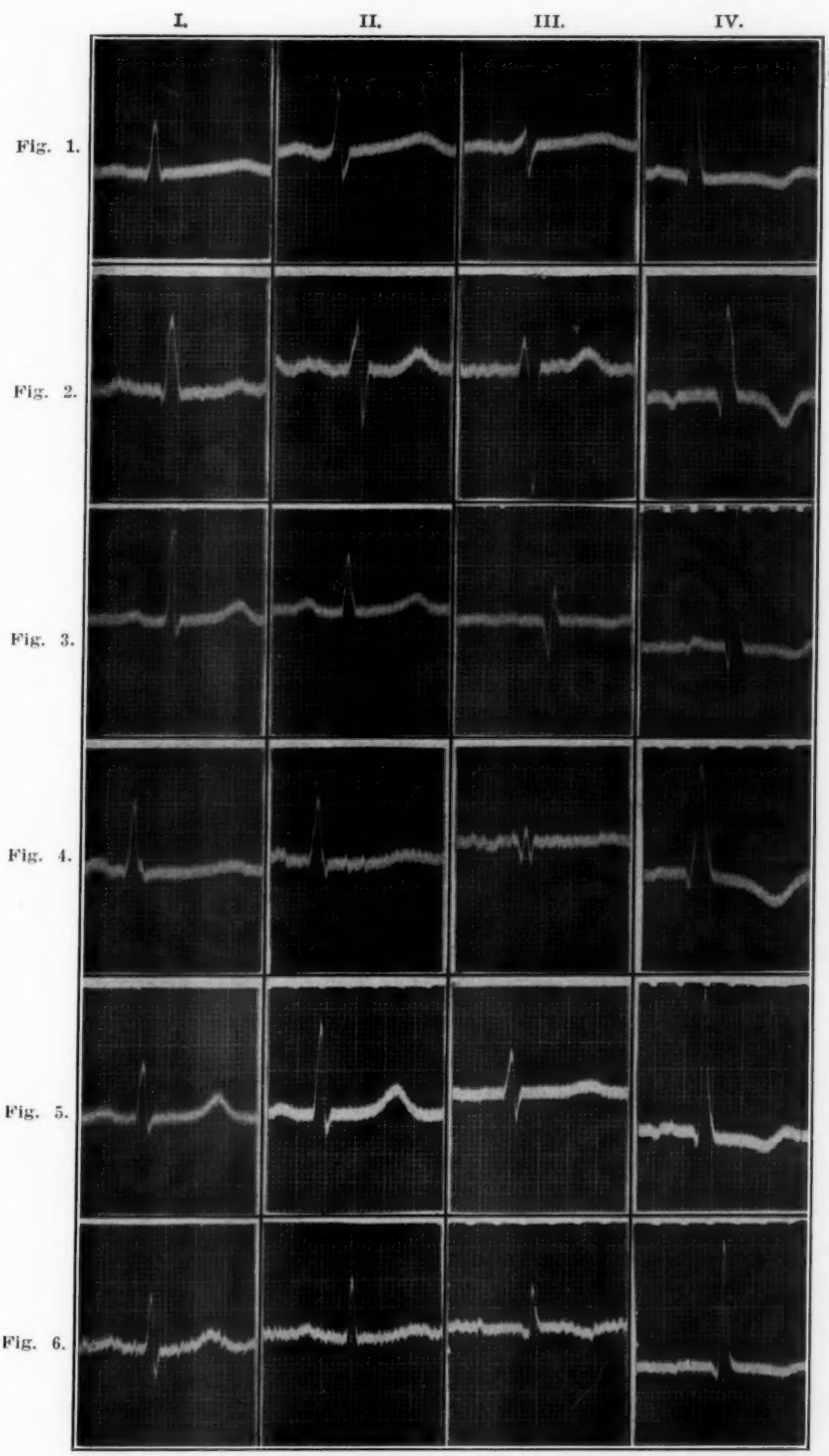

PLATE A. *(See legends on opposite page.)*

this to be either higher or lower. However, it is possible to approach the subject from another angle, the problem being: Why and when is left axis deviation absent in hypertension? In our opinion it is possible to understand in most cases the absence of left axis deviation in extremity leads by comparing the curves of the standard leads with those of the thoracic lead, which is taken in an altogether different plane (sagittally); conversely, the same holds for cases in which left axis deviation is absent in the thoracic lead, while it is present in the leads from the extremities; finally it is possible with the data from these groups to investigate the absence of left axis deviation in all leads in cases of hypertension.

Left Axis Deviation Only in Thoracic Leads (36 Cases, Figs. 3-10)

In case left axis deviation occurs only in thoracic leads (shallow Q or absence of Q, high R), the ventricular complexes in the standard leads appear to be:

1. Deformed by deep, sharp notches (Case 9, Fig. 9). This then is a plausible reason for the nonmanifestation of left axis deviation in cases of distinct hypertension.

2. Normal. In these cases the heart did not appear dilated in the roentgenogram, However, an incipient dilatation often takes place in

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PLATE B

II. Left Axis Deviation in Lead IV Only

Fig. 7.—Woman, aged fifty-two years, hypertension (160/115), dyspnea on exertion, swollen ankles in the evening, palpitation. X-ray examination of the heart: curved arch of left ventricle; however, no enlargement (12.5 cm.). Electrocardiogram: prolongated S-T segment (0.40 sec.). Lead III: small, notched complexes, T positive. Lead IV: left axis deviation (small Q, high R-wave). S-T isoelectric. T shallow in relation to R. Conclusion: the hypertension causes left axis deviation in Lead IV only, early dilatation of the heart. Prolongated S-T segment and shallow T_4 show that the myocardium is not in optimal condition.

Fig. 8.—Man, aged forty years, verrucous endocarditis of the aortic valves. Aortic regurgitation. Tension 150-0. Diameter of the heart, 15.6 cm. Electrocardiogram: low T-wave in Lead I. Lead II: anisoelectric S-T notch at the foot of RS. Lead III: notched complexes. Lead IV: left axis deviation (small Q, high R-wave). The negative P-wave is clearly visible in the positive T-wave. A-V conduction time 0.26 sec. Conclusion: multiple signs of myocardial damage. Left axis deviation in Lead IV only.

Fig. 9.—Woman, aged forty-four years, thyrotoxicosis. Tension 160/95. Heart, 12.9 cm. Electrocardiogram: in Leads I and II, split P-waves; in Lead III notched complexes; in Lead IV left axis deviation (shallow Q, high R-wave). Further on, auricular extrasystoles.

Fig. 10.—Woman, aged twenty-one years, hypertension (150/110). Vagovasal attacks. Bronchial asthma. Heart not enlarged (13 cm.). Electrocardiogram: in standard leads rather right than left axis deviation. In Lead IV, according to hypertension, left axis deviation. S-T segment at first horizontal. Conclusion: left axis deviation, no evidence of myocardial damage.

III. Left Axis Deviation in Standard Leads Only

Fig. 11.—Man, aged fifty-three years, seizures of unconsciousness, complains of palpitation, tingling in arms and legs. Marked peripheral arteriosclerosis. Blood pressure 145/80. Heart enlarged to the left (diameter, 15.5 cm.), broad aorta. Electrocardiogram: in standard leads left axis deviation. T_3 negative. In Lead IV typical shape of coronary sclerosis, deep Q-wave (–20 mm.), low R-summit (5 mm.), deep and somewhat broad T-wave (–11 mm.). Coronary sclerosis masks, according to our conception, left axis deviation in Lead IV.

Fig. 12.—Man, aged sixty-eight years, diabetes, sclerosis of aorta, and peripheral sclerosis. Wassermann reaction negative. Tension 145/70. Heart enlarged to the left. Electrocardiogram: auricular extrasystoles (bigeminy). No left axis deviation in Lead IV: deep Q-wave (–19 mm.), low R-wave (12 mm.), deep negative T-wave, in which the P-wave of the next auricular extrasystole is just visible.

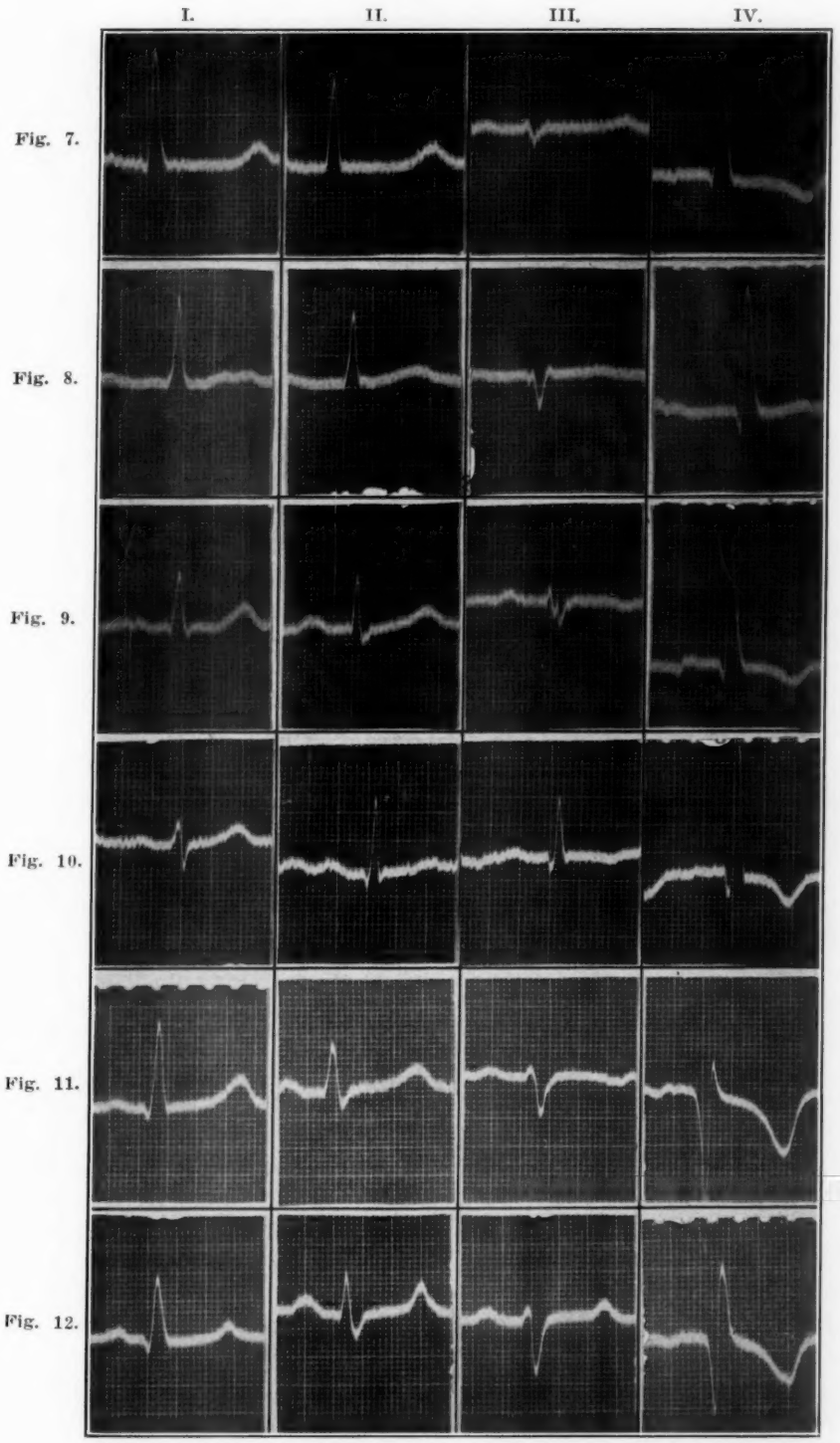

PLATE B. *(See legends on opposite page.)*

the sagittal plane, in other words, in the plane of the thoracic lead; only in more pronounced stages of dilatation it is accompanied by a rotation, which places the left ventricle more and more in the frontal plane; for this reason the left axis deviation in the beginning manifests itself only in the thoracic lead. In radioscoping these cases, attention should be paid to a posterior enlargement of the left ventricle by observing the patient in the second oblique position (Case 5, Fig. 5).

3. Changed as a result of abnormal conditions of the coronary arteries. These occurred very often in this group. Eleven times we found a so-called Pardee-Q in Lead III and eight times an *M*- or a *W*-shaped ventricular complex. The extensive investigations of Pardee, Edeiken, and Wolferth[19] and Wallace[20] have proved beyond doubt that a deep Q in Lead III, complying with Pardee's[21] criteria, is characteristic of coronary sclerosis (and when it is seen to establish itself in successive electrocardiograms, for coronary thrombosis[22]). We as well as others are of the opinion that the *M*- and *W*-shaped ventricular complexes are often due to coronary sclerosis. Although this type of change in Lead II is practically sure to have a definite significance (Edeiken and Wolferth[23]), its occurrence in Lead III, especially in advanced age, points to the diagnosis of coronary sclerosis. In addition to the pathological data on which the above mentioned research is based, we have further support in the anamnesis of these patients in whom angina pectoris is often found. In this group of thirty-six patients we found eight with angina pectoris.

Peripheral arteriosclerosis could be demonstrated in fourteen out of the nineteen cases in which a Pardee-Q or *M*- or *W*-shaped ventricular complex was found. Furthermore, a saddle-shaped S-T curve occurred fifteen times in Lead I or II separately, an abnormality which in its pure form* is almost exclusively found in cases of coronary sclerosis.

Summarizing.—Left axis deviation is absent in the standard leads and present in the thoracic leads (1) because notches resulting from injury of the myocardium conceal the left axis deviation in standard leads (Case 2, Fig. 2), or (2) because of the dilatation of the left ventricle still taking place in the sagittal plane only (Case 3, Fig. 3), or (3) because coronary sclerosis alters the ventricular complexes in Leads I, II and III, thus covering up the left axis deviation (Cases 4 and 5, Figs. 4 and 5).

Left Axis Deviation in Standard Leads Only (Figs. 11-15)

In 25 cases we found a marked left axis deviation in the Leads I-III, while in Lead IV the Q-wave was not shallow or absent, but distinctly too deep (from –7 to –18 mm.). Of the patients showing these cardiograms, 25 were over fifty and 12 over sixty years old; 8 suffered from angina pectoris, and in 14 other cases arteriosclerosis could be diagnosed (pulse, aorta, retina). Thus 17 out of 25 patients had arteriosclerosis.

*We intend to revert to this subject in another paper (on coronary sclerosis).

Eleven of these showed a saddle-shaped S-T curve in Lead I or II; seven, a remarkable, steep S-T curve beginning below the isoelectric level; two patients suffering from an after-effect of acute nephritis were fifteen and seventeen years old respectively; in these cases a deep Q_4 can be attributed to a vertical position of the heart, which existed in both patients (in a preceding paper we have shown that a shallow or positive T and a low Q are normal in children and asthenic subjects[24]). When x-ray pictures were taken, they showed a distinct dilatation of the heart in all but two cases. The heart was normal in size in one patient with angina pectoris (blood pressure 135/70) and in one of the patients who had had acute nephritis (blood pressure 165/60). Finally in a patient with bronchiectasis the heart was markedly displaced toward the right (the man was thirty-one years old, blood pressure 115/70).

Thus the absence of left axis deviation in the thoracic lead, although plainly evident in the standard leads, may be accounted for by:

1. The age of the patient, because in youth a low Q_4 can be normal (Case 13, Fig. 13).

2. A distortion or displacement of the heart toward the right.

3. Arteriosclerotic changes in the coronary vessels and their results (Cases 11 and 12, Figs. 11 and 12).

4. A mitral insufficiency coinciding with the hypertension (Case 10, Fig. 10) and a deep Q_4 regularly occurring in mitral stenosis and insufficiency.

Hypertension Without Left Axis Deviation in Standard and Thoracic Leads (Figs. 14-17)

This we saw in thirty-two of the cases studied. The abnormal conditions, as described for the above groups, can also be found in this group. An *M*- or a *W*-shaped ventricular complex in five cases, a Pardee-Q in seven cases, and a notched ventricular complex in ten cases concealed the left axis deviation in the standard leads; the Q in the thoracic lead was usually deep, sometimes normal, but never shallow in these cases. In four cases the standard leads were normal and the Q deep (–8 to –10 mm.). In four of the other six cases of distinct hypertension a marked dilatation could not be demonstrated by radioscopy (Dl ÷ Dr not exceeding 12.5 cm.); a mitral stenosis accompanied by hypertension occurred once (155/75). In the other case we found a hypertension of 195/80 with a normal electrocardiogram, while the heart appeared to be slightly dilated toward the left.

As a result of these observations we can say that absence of left axis deviation in the standard and thoracic leads in cases of marked hypertension is usually caused by (1) abnormal conditions in the coronary system concealing the left axis deviation; (2) notches distorting the ventricular complexes; and (3) a normal shape of the heart notwith-

standing the hypertension; in these cases it seems only reasonable to assume that the hypertension has not existed very long or is not constantly present.

Up to this time a direct relation between left axis deviation and hypertension has been considered to be doubtful. The results of statistics on 238 patients formed the basis of our hypothesis—that left axis deviation depends on a dilatation of the left half of the heart, beginning in a sagittal plane (in which stage a left axis deviation can be recorded in the thoracic leads only) and later on also in the frontal plane, the heart rotating clockwise on its longitudinal axis; in those cases left axis deviation is usually recorded in the standard leads too. Left axis deviation is generally not seen when no dilatation exists.

Absence of left axis deviation in hypertension which has brought about a heart dilatation is in our opinion caused by other factors which conceal the left axis deviation in these cases; thus the electrocardiogram is influenced by coronary defects (Pardee-Q, *M*- or *W*-shaped ventricular complexes, saddle-shaped S-T curve and, in the thoracic lead, a deep Q, with a low R and the S-T curve horizontal at first, instead of the normally existing absence of an isoelectric S-T curve in this lead), or by a change of position of the heart, by notches distorting the ventricular complexes, by the tendency to right axis deviation in mitral defects, and by age (a deep Q_4 is normal in youth). The absence of left axis deviation on the electrocardiograms of patients with hypertension calls for a search of the interfering factors mentioned above.

PLATE C

III. Left Axis Deviation in Standard Leads Only

Fig. 13.—Boy, aged seventeen years, postanginous nephritis. Tension 155/85. Electrocardiogram: left axis deviation in standard leads. In Lead IV deep Q-wave, such as is commonly seen in adolescence and as a rule in childhood. Heart diameter, 11 cm. An example of the remaining of a deep Q-wave in youthful patients in spite of hypertension.

IV. Left Axis Deviation Fails in All Leads

Fig. 14.—Woman, aged forty years, precordial pain and dyspnea on exertion. Tension 160/85. Wassermann reaction, negative. Heart slightly enlarged to the left, hypertension type. Electrocardiogram: in Lead I diphasic T, S-T segment runs below the isoelectric level. Lead II: somewhat saddle-shaped S-T segment. In Lead III a Pardee-Q. Lead IV: small, notched complexes. T positive: the shape reminds one of the C_1 type and originates here probably from arteriosclerotic changes of the right coronary artery. These are masking left axis deviation in all leads.

Fig. 15.—Woman, aged forty-four years, mitral stenosis. Tension 155/75. Heart enlarged to the left (13.4 cm.). In spite of hypertension and left dilatation, no left axis deviation. (Deep Q_4, normal S and R summits in standard leads.)

Fig. 16.—Woman, aged forty-eight years, chronic Bright's disease. Tension 210/160. Heart of normal shape, not enlarged to the left (12.5 cm.). The electrocardiogram shows no typical changes. Notwithstanding the hypertension the failure of left axis deviation conforms to the normal heart diameter.

Fig. 17.—Woman, aged sixty-six years, hypertension 225/110. Peripheral arteriosclerosis, arteriosclerotic retinitis. Heart enlarged to the left (Dr 4, Dl 10 cm.). transverse type, aortic knob prominent. Urine: no abnormalities. Electrocardiograms: saddle-shaped S-T segment in all leads. In chest lead S-T almost horizontal. In Lead III notched *M*-shaped complexes; Lead IV: coronary sclerosis type (deep Q-wave, relatively low R summit, almost horizontal S-T line). Conclusion: notwithstanding hypertension and dilatation of the heart, no left axis deviation as a consequence of coronary sclerosis.

V. Left Axis Deviation in All Leads; T_1 Negative, T_3 Positive, No Convexity of S-T Segment in Lead I

Fig. 18.—Woman, aged fifty-one years, hypertension (275/170). Apoplexy, cardiac failure. Electrocardiogram: pronounced left axis deviation, S-T segment not evidently convex in Lead I, in Lead III slightly concave.

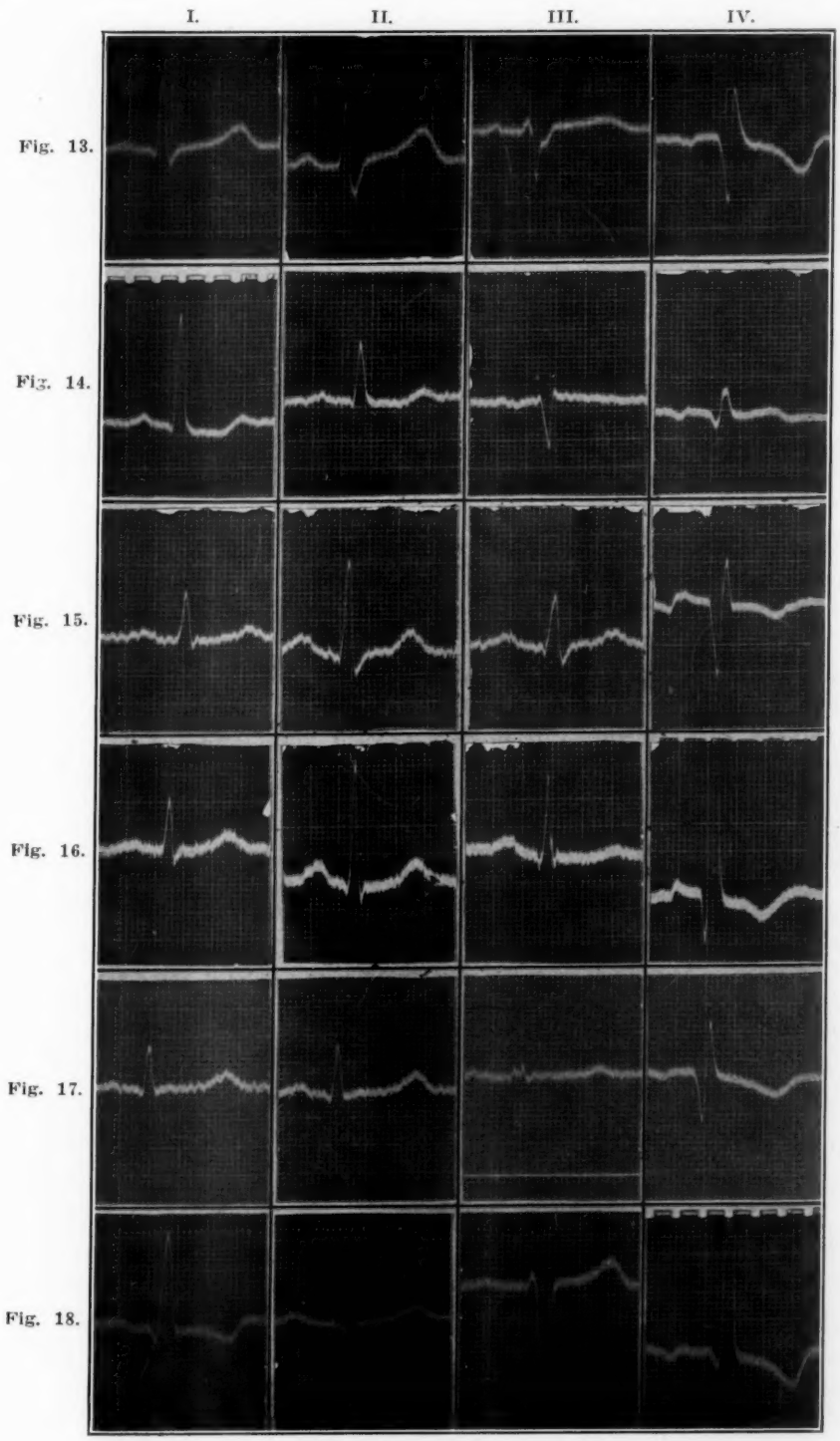

PLATE C. *(See legends on opposite page.)*

II. THE SIGNIFICANCE OF THE NEGATIVE T-WAVE IN LEAD I AND OF THE POSITIVE T-WAVE IN LEAD III IN CASES OF LEFT AXIS DEVIATION ON THE ELECTROCARDIOGRAM (FIG. 18)

A divergence of opinion has long existed about this phenomenon. Are these T-waves, opposite to the main deviation of the electrocardiogram, caused by the left axis deviation as such, that is, by a change of position of the anatomical or of the electrical axis of the heart, or are the negative T_1 and the positive T_3 an indication of an imperfect condition of the myocardium? This is a problem of clinical importance. The same problem applies to the positive T_1 and the negative T_3 in electrocardiograms with right axis deviation.[25] Barnes and Whitten[26] as well as Wilson and Herrmann[27] support the first theory; Freundlich[28] and Proger and Minnich,[29] the second one. We agree with the opinion that in hypertension a negative T-wave in Lead I indicates an imperfect condition of the myocardium. This is what experience teaches us. But also it is hard to explain how a negative T_1 could be brought about by a left axis deviation. As we have set forth already, one would sooner expect an altered position of the electrical or anatomical axis to cause a total inversion of the ventricular complex[30] (the T-wave moving in the same direction as the main deviation of the ventricular complex). In considering the similar diphasic character of the waves in the bundle-branch and arborization block, a possible explanation was sought in intraventricular conduction disturbances. We have mentioned already that an extended QRS complex is hardly ever found in hypertension curves.

The results of our comparison of patients with a positive T_1 in the electrocardiogram and patients with a negative T_1 are given in Table VII.

TABLE VII

	T_1 POSITIVE	T_1 NEGATIVE
Number of cases	91	62
Symptoms of cardiac failure	26%	70%
Anginal complaints	20%	26%

Although patients with a positive T_1-wave often show a more markedly dilated heart than patients with a negative T_1, in our cases we often found a mild hypertension coinciding with a negative T_1 and a higher tension still showing a positive T_1.

Whatever the explanation may be, the experience from our cases has taught us that symptoms of decompensation occur more often when hypertension coincides with a negative T_1 and a positive T_3 than with a positive T_1. This fact alone is of clinical interest.

(For the significance of the T-wave in Lead IV, see "V. Electrocardiographic Differential Diagnosis.")

III. THE CONVEXITY OF THE S-T CURVE IN LEAD I AND THE CONCAVITY OF THE S-T CURVE IN LEAD III IN HYPERTENSION (FIGS. 19-21).

In studying the curves of patients with hypertension, we repeatedly found these remarkable abnormalities: The convex S-T curve in Lead I as a rule continued into a negative T-wave, and the concave S-T curve into a positive T. In most of these cases we noticed serious heart trouble. The phenomenon occurred twice as often in subjects over fifty years of age as in those under fifty years; it was seldom seen in subjects with tensions under 150 mm. but was seen frequently in subjects with tensions over 200 mm. Hg. In practically all cases the heart was dilated toward the left, Dl amounting to more than 11 cm. in 75 per cent of the cases. In more than half of the cases distinct cardiac failure was found, and in one-third of all cases the anamnesis included anginal complaints. In patients with tension above 200 mm. the convexity of the S-T line occurred twice as frequently as left axis deviation without this abnormality. Furthermore, the group with the convex S-T curve usually showed a greater dilatation of the heart toward the left than the other group and, finally, a slightly higher incidence of cardiac failure was seen than in the other group.

Here too the question arises whether the convexity of the S-T curve in Lead I is a result of the cardiac dilatation as such, or of the poor condition of the heart muscle. Finding a distinct enlargement of the heart toward the left far more often than in the group without a convex S-T curve while the incidence of heart decompensation increased in a lesser degree, we are inclined to interpret the convex S-T curve as a manifestation of the heart enlargement itself. Those patients showing a convex S-T curve in Lead I and a tension under 150 mm. Hg nearly always suffered from aortic regurgitation, in which the heart was greatly dilated, although real symptoms of cardiac failure were usually absent.

TABLE VIII

	LEFT AXIS DEV. WITH CONVEX S-T CURVE	LEFT AXIS DEV. WITHOUT CONVEX S-T CURVE
Number of cases	76	98
Men	45%	45%
Women	55%	55%
Over 50 years of age	63%	67%
Systolic tension 145/200 mm. Hg	30%	44%
Systolic tension 200/250 mm. Hg	50%	23%
Systolic tension 250/300	11%	3%
Heart distinctly dilated toward the left (Dl + Dr 16 cm.)	75%	28%
Symptoms of cardiac failure	55%	40%
Anginal symptoms	30%	22%

Comparing a group of cases of left axis deviation with a convex S-T curve to a group without a convex S-T curve, both groups, however,

showing a negative or diphasic T_1, practically the same percentage of cases of failure is found, as is shown in Table IX.

TABLE IX

	CARDIAC FAILURE	ANGINA PECTORIS
S-T convex, T_1 diphasic or negative	64%	31%
S-T not convex, T_1 diphasic or negative	68%	26%

Rijkert and Hepburn published a paper on the convexity of the S-T curve[31] some time after we had started our studies on this subject. These authors also found the convex S-T curve practically always present in arterial hypertension, while the cases showing no hypertension had aortic regurgitation or aortic stenosis. They found failure in 57 per cent of the cases, a figure remarkably close to our result (55 per cent). On these grounds, they point out the clinical importance of this defect, but they omitted to compare their cases with a group of cases of left axis deviation without a convex S-T curve. Such a comparison shows the percentage of patients with failure to be not much higher than in the group without a convex S-T curve. In 14 out of 20 patients examined after death, they found coronary lesions (sclerosis, atheromatosis and, in one case, thrombosis). This percentage is not surprising in this group considering the fact that hypertension so often coin-

PLATE D

VI. Convexity of S-T Segment in Lead I, Concavity in Lead III, Convexity in Lead IV

Fig. 19.—Man, aged sixty-seven years, tension 220/110. Angina pectoris. Heart of transverse type. Urine, normal. Electrocardiogram: low T_1, left axis deviation in all leads. Marked convexity of S-T line in Lead IV.

Fig. 20.—Man, aged forty-one years, chronic Bright's disease. Tension 230/165. Heart strongly enlarged to the left. Electrocardiogram: marked left axis deviation. Obvious convexity of S-T in Lead I, concavity in Lead III. S-T runs in Lead I below, in Lead II above isoelectric level. In addition, negative T_1, and positive T_3.

Fig. 21.—Man, aged forty-two years, syphilitic aortic regurgitation. Cardiac failure. Heart strongly enlarged to the left. Electrocardiogram: pronounced left axis deviation in all leads. Convexity of S-T interval in Leads I, II, and IV. S-T_3 straight, ascending.

VII. Pronounced Convexity of S-T Line in Lead IV, With S-Wave, in Extensive Injury of the Kidney (Nephrosclerosis)

Fig. 22.—Woman, aged sixty-six years, diabetes mellitus, severe angina pectoris, gangrene of toes. Tension 220/115. Heart enlarged to the left. Electrocardiogram: in Lead I, S-T runs below the isoelectric level and in convex. T_1 is diphasic. In Lead II notches in QR, T-wave diphasic. A-V time 0.18 sec. Lead III: distinct Pardee-Q, S-T runs above isoelectric level. Lead IV: pointed convex S-T line, T negative. On this score a diagnosis of coronary sclerosis and extensive damage to the kidneys was made. Sudden death. Post-mortem examination: severe coronary sclerosis. Thrombosis of a branch of the left descendent coronary artery, arteriosclerotic nephrosclerosis.

Fig. 23.—Man, aged forty-five years, entered hospital with symptoms of acute myocardial infarction. Was known to be suffering from kidney disease. Tension, on entering the ward (when cardiac failure already existed), 125/65. Urine, albumin 0.3 per cent, numerous hyaline and granular casts. No x-ray examination. Electrocardiogram: in Lead I small, notched complexes, S-T runs a little above the isoelectric level and is slightly convex, indication of Pardee RS-T segment. Lead II: S-T segment lies below isoelectric level, diphasic T-wave. Lead III: deep S-wave, S-T below isoelectric level, diphasic T-wave. Lead IV: C_2 type; in addition a convexity of the S-T line is to be noted. A distinct S-wave exists in this lead. Diagnosis: anterior infarction, nephrosclerosis (?).

Fig. 24.—The patient declined rapidly, cardiac failure increased, auricular fibrillation occurred, at first in paroxysms, later on continuously. The patient died with the symptoms of severe failure. Post-mortem examination: dissecting aneurysm of the whole aorta, anterior infarction, genuine nephrosclerosis.

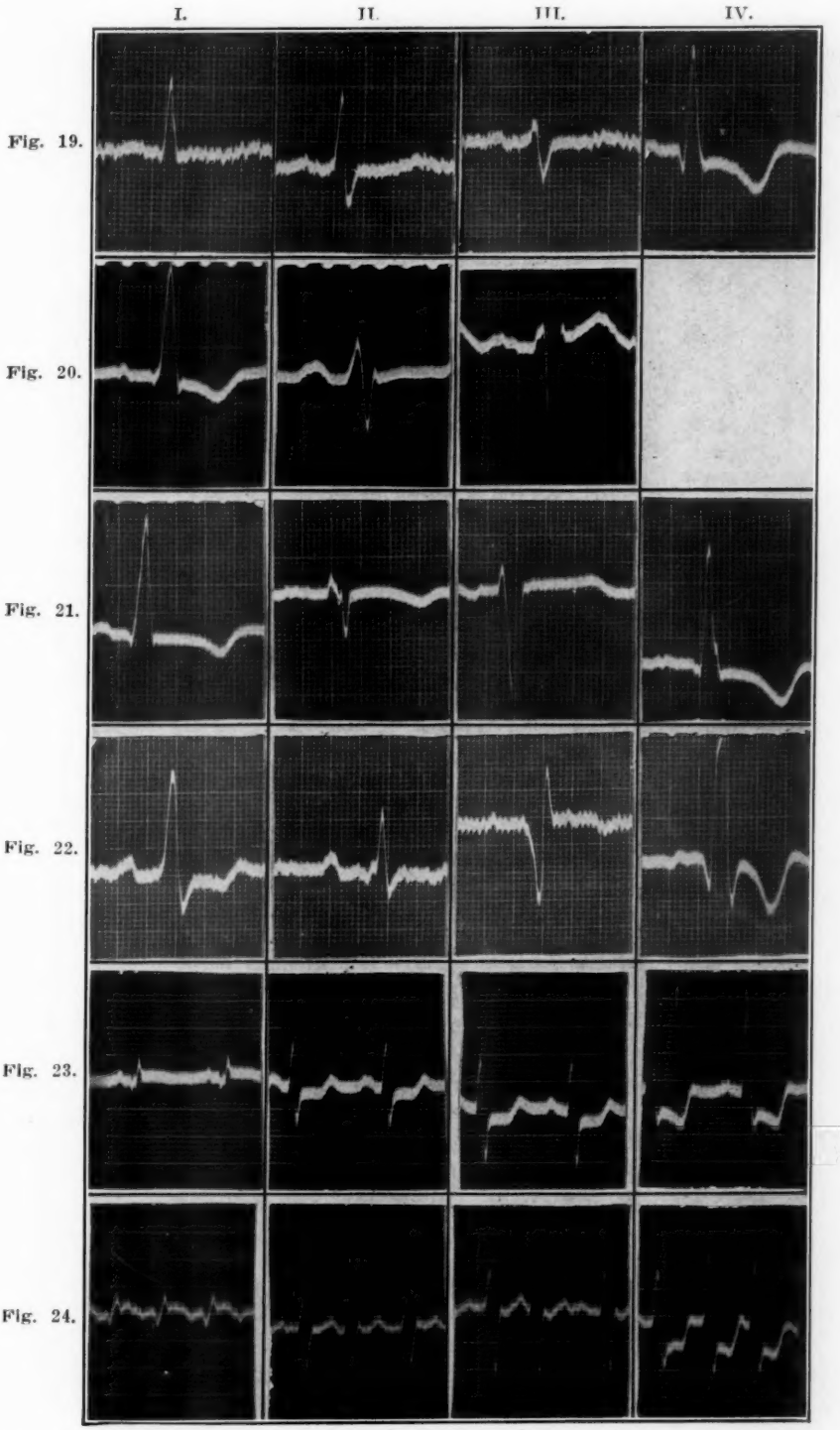

PLATE D. *(See legends on opposite page.)*

cides with arteriosclerosis and that coronary sclerosis is found so often at post-mortem examination of patients who have suffered from hypertension (90 per cent, Nuzum, Elliot and Evans;[32] 50 per cent, Rössle; 40 per cent, Bell and Clawson[33]).

Necropsy also showed coronary lesions in some of our cases; in some other cases, however (e.g., with chronic nephritis), these could not always be demonstrated. We came to the conclusion that coronary changes could not always be considered to be the cause.

To summarize, then, we have found that:

1. The convex S-T curve in Lead I and the concave S-T curve in Lead III usually occur in cases of hypertension; in the absence of hypertension these electrocardiographic deviations are usually manifestations of aortic defects; often they are very clearly seen in cases of chronic nephritis (see also V).

2. The cause of these changes is to be found in the marked dilatation of the heart; coronary troubles may have an influence.

3. Since a convex S-T curve usually occurs in cases of pronounced dilatation, the symptoms of failure are naturally frequent; however they may be absent (compensated defects of the aortic valves).

IV. THE OCCURRENCE OF AN S-WAVE, FOLLOWED BY AN EXTREME CONVEXITY OF THE S-T CURVE IN LEAD IV (FIGS. 22-24)

Normally an S-wave is not found in Lead IV and the S-T curve starts at, or at most, 2-2.5 mm. below the isoelectric level, proceeding continuously into the negative T-wave without a horizontal stretch.

A few of the curves, however (we have seen four tracings up to this time), showed a marked S-wave and a distinct convexity of the S-T curve. All patients showing this phenomenon were very ill, the clinical diagnosis being uremia in two, coronary thrombosis and coronary sclerosis in one each. In three cases a post-mortem examination was made. In the patient with coronary thrombosis (Case 23, Fig. 23), in addition to the heart infarction which had caused the C_2 type (the other leads did not point positively to the diagnosis of coronary thrombosis), a pronounced nephrosclerosis was found. We had anticipated this, as the descending part of the S-T line was unusually convex for a C_2 type. A post-mortem examination of the patient with coronary sclerosis revealed a thrombosis adherent to the arterial wall. The blood could still pass the ramus descendens of the arteria coronaria sinistra, for which reason an infarct had not developed. In addition, a serious nephrosclerosis was found. In a third case of uremia we also found extensive alterations in the kidneys. We are not able as yet to explain the origin of this type. Hypertension was found in three cases; the heart was dilated in all cases, although not always considerably. Whatever the cause may be, this type, which is rather rare (4 out of 2,000 electrocardiograms), is probably an indication of extensive alterations in the kidneys.

V. ELECTROCARDIOGRAPHIC DIFFERENTIAL DIAGNOSIS

On first view the electrocardiogram in hypertension, especially when the T-wave in Lead I is negative, may be mistaken for the electrocardiogram of coronary thrombosis; in this case it also looks similar to the electrocardiogram of arborization and bundle-branch block. As for the bundle-branch block, diphasic ventricular complexes, usually of a high voltage, occur in both types. On the other hand, notches in the ventricular complexes and an increased Q-S interval are obligatory signs of the bundle-branch and arborization block, while notches are hardly ever, a prolonged ventricular complex practically never, found in the electrocardiogram in cases of left axis deviation. Moreover, these two electrocardiograms differ in the thoracic lead, in which arborization block, in addition to the prolonged and notched ventricular complex, shows a deep, pointed T-wave, and the bundle-branch block, a deep obtuse T-wave; while the T-wave is usually normal or slightly too low in cases of hypertension. Exceptionally these latter cases too show a deep T-wave which, however, is associated with a deep, and not a shallow or absent, Q-wave in the ventricular complex.

The electrocardiogram in thrombosis of the left coronary artery followed by an anterior infarct, which in Lead I sometimes causes a convex, high take-off of the S-T segment with the T-wave creeping into it (Smith, Pardee), changes in the course of time (two to four weeks) into a type in which S-T starts at the isoelectric level and continues after a rather long isoelectric course into a negative T-wave, which is comparatively narrow and shallow itself. On first view this electrocardiogram resembles that of a case of hypertension with a negative T_1. However, the types with the convex S-T line do not present any differential diagnostic difficulties; in the first place because in hypertension R_1, after T_1 has become negative, is usually high (exceeding 12 mm.), while in the electrocardiogram of coronary thrombosis R_1 is low. Furthermore, in Lead IV the tracings are totally different. In cases of anterior infarction the C_2 type (a long descending S-T limb, continuing into a short ascending limb, forming an angle of about 125° between them) usually occurs, which S-T segment differs altogether from the blunt, low or pointed T-wave in the bundle-branch and arborization block. In aortic regurgitation, however, it is quite possible that the electrocardiogram in the chest lead may resemble the C_2 type. In both cases the Q-wave is small or absent, the R-wave high. However, in coronary thrombosis the S-T line as a rule (not always) has its starting point far below the isoelectric level, and a positive T-wave, such as usually appears in the C_2 type of coronary thrombosis, never occurs in aortic regurgitation. In addition, the C_2 type usually shows a notch (the size of which depends on the location of the electrode), while in regurgitation this is often absent. The descending S-T segment is practically always straight in coronary thrombosis, and invariably convex

in aortic regurgitation. However, in view of the marked similarity between the tracings as obtained in the thoracic lead, especially in luetic aortic regurgitation and those in anterior infarction, the question presents itself whether in aortic regurgitation, too, the coronary circulation has not decreased (by luetic changes of the intima or coronary stenosis). The anginal complaints in aortic regurgitation point in the same direction.

SUMMARY

In hypertension the *extremity leads* may show:

1. Left axis deviation alone;

2. Left axis deviation, with a negative T_1 and a positive T_3—usually in cases with myocardial damage;

3. Left axis deviation, with a negative T_1, a positive T_3, a convex S-T_1 interval and a concave S-T_3 interval. In such cases the heart usually shows pronounced dilatation;

4. Absence of left axis deviation, as a consequence of factors mentioned below.

Lead IV shows usually the following characteristics: P-wave diphasic; Q, shallow or absent; a normally wide ventricular complex; R-wave, high; T-wave, rather low, negative and of normal shape; no notches usually. When, however, the hypertension is due to aortic insufficiency, the S-T segment has a long, convex descending limb and a short ascending one. When the hypertension is complicated by coronary sclerosis, then instead of a small or an absent Q-wave, this wave is usually deep; the R-wave, low; the S-T interval, isoelectric in its first portion; and the T-wave, negative and deep. However, many variable forms are seen. In a few cases of hypertension associated with nephrosclerosis we found a deep S-wave (–5 to –7 mm.) continuing into a distinctly convex S-T interval which, after returning to the isoelectric level, ended in a deep, negative T.

Ziskin concludes his paper, published in 1928, with the words: "Other factors, besides those enumerated, and a present unknown, are involved in the production of left ventricle pre nderance." Since then eight years have passed in which extensive research work has been done to investigate the condition of the myocardium and the coronary vessels by means of the electrocardiogram.

Using as routine a thoracic lead in addition to the standard leads, we were able to draw conclusions not only from the similarities, but especially from the differences between them. This brought out the fact that in hypertension left axis deviation is present in 83 per cent of the cases in standard or chest leads, for which in our opinion not only the clockwise rotation in the longitudinal axis, but especially the enlargement of the heart must be held responsible. We based our experiments on the assumption that left axis deviation, when absent in

marked cardiac dilatation, is obscured by interfering factors. Certain factors were found to cause this absence; e.g., in youth, the longitudinal position of the heart, notwithstanding dilatation; the enlargement in a sagittal plane only, in incipient cases; and finally, in advanced age, coronary sclerosis. Therefore the absence of left axis deviation in a case of marked enlargement of the heart should lead one to suspect some of the above mentioned conditions.

A negative T_1 and a positive T_3 were found to imply an involvement of the myocardium. The convex S-T_1 interval and concave S-T_3 interval, which in our opinion are caused by the pronounced cardiac dilatation accompanying these cases, should therefore suggest, usually, a doubtful prognosis.

We have drawn attention to a special type of the ventricular complex in Lead IV, in which an S-wave and an extremely convex S-T interval are conspicuous; in these cases serious kidney damage was found (nephrosclerosis, chronic nephritis).

Finally, we have described in detail the electrocardiogram in cases of hypertension and its differential diagnostic difficulties, giving the chest lead especial attention.

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CORONARY THROMBOSIS: AN INVESTIGATION OF HEART FAILURE AND OTHER FACTORS IN ITS COURSE AND PROGNOSIS*†

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THE more recent studies of coronary artery thrombosis have brought out the importance of the rôle of cardiac insufficiency in determining the course of this disease.[1, 2, 3] Early writers[4, 5] attributed many of the symptoms of coronary thrombosis other than precordial pain and shock to passive congestion secondary to ventricular damage. Levine[6] found that in a large group of his patients the temporary improvement following the immediate effects of the thrombosis was succeeded by symptoms of progressive congestive heart failure, which, when they persisted for weeks, assumed an ominous significance. In our series we found a high incidence of congestive failure, particularly in the fatal cases, and in a number of our patients the sudden appearance of congestive failure or the sudden aggravation of preexisting failure was the only indication of coronary artery occlusion. Similar cases of coronary occlusion have probably been unrecognized in the past, although some have been reported.[2, 6, 7]

We have tried to determine the factors that predispose to cardiac insufficiency in acute coronary artery thrombosis and to evaluate the prognostic significance of the various signs and symptoms related to such insufficiency.

Since coronary thrombosis is predominantly a lesion of the left ventricle, it seemed desirable to utilize the concept of left versus right heart failure. That is, when the strain on the left ventricle induced by infarction is sufficiently severe, this chamber fails, resulting in back pressure in the pulmonary circuit and stasis in the lungs. The clinical picture of left ventricular failure thus presented was described first by Hope[8] and later by other authors in Europe.[9-13] In this country the principle has been discussed more recently by Hirschfelder,[14] Robb and Weiss,[15] White and McGinn[16] and Fishberg;[17] lately, Fishberg, Hitzig and King[2] have applied it to coronary thrombosis. Failure of the left ventricle alone is characterized by dyspnea, orthopnea, ashen gray cyanosis, cough, bloody expectoration, cardiac asthma, pulmonary râles or edema, diastolic gallop rhythm, accentuation of the second pulmonic sound, diminished vital capacity, and prolonged arm-to-

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†Read at the meeting of the American Heart Association, Kansas City, Mo., May 12, 1936.

tongue circulation time. When the strain further involves the right ventricle or often initially, if infarction of the interventricular septum occurs, evidence of failure of the right ventricle appears in the form of bluish cyanosis, distended cervical veins, hydrothorax, enlargement of the liver, ascites, edema, increased venous pressure and prolonged arm-to-lung circulation time. A combination of both types of failure usually occurs in coronary thrombosis. White and McGinn[16] have emphasized the fact that initial strain of the left ventricle is responsible not only for the majority of cases of failure of this ventricle alone but of both ventricles combined. In coronary thrombosis, the primary strain is, of course, almost always on the left ventricle.

INCIDENCE AND MORTALITY RATE

This study is based on 140 consecutive ward cases of coronary artery thrombosis (Table I). Cardiac insufficiency was present in two-thirds of the patients; 18 per cent had evidence of left ventricular failure alone and 48 per cent of left and right combined. Isolated heart failure of the right ventricle did not occur. It has been observed that when the heart fails following coronary occlusion, the right ventricle, in addition to the left, usually becomes insufficient. In a previous series studied by Master[1] nearly all the cases showed definite heart failure, usually both left and right. Analysis of the circulatory measurements in coronary thrombosis published by Fishberg and his coworkers[2] indicates similar findings, particularly in the severe and fatal cases. It is interesting to note that while the infarction nearly always involves the left ventricle alone, the cardiac failure which results is usually failure of both left and right ventricles.

TABLE I

INCIDENCE OF HEART FAILURE IN 140 ATTACKS

	FIRST ATTACK	SECOND	THIRD	FOURTH	ALL ATTACKS
No. of cases	74	48	16	2	140
Cardiac failure	39 (53%)	38 (79%)	14 (88%)	2	93 (66%)
Left only*	11 (15%)	12 (25%)	3 (19%)	0	26 (18%)
Left and right†	28 (38%)	26 (54%)	11 (69%)	2	67 (48%)
Mortality rate	8 (11%)	14 (29%)	8 (50%)	0	30 (21%)

*Left ventricular failure.
†Combined left and right ventricular failure.

Cardiac insufficiency occurred in 93 of our 140 cases. It appeared with equal frequency in men and women (Table II) although in this series there were four times as many men as women. The type of failure and the mortality rate were similar for both. The average age of patients with cardiac insufficiency was fifty-seven years, which exceeds by eight years those without failure (Table II). This difference is probably the result of the more advanced involvement of the coronary arteries in the older patients. However, even young patients

developed severe heart failure if the infarction was extensive. The average age of the patients with left heart failure alone was practically the same as that of the patients with combined left and right heart failure.

TABLE II

SEX AND AGE IN HEART FAILURE

	MALES	FEMALES	TOTAL	AVERAGE AGE
No. of cases	111	29	140	54 yr.
Cardiac failure	75 (68%)	18 (62%)	93 (66%)	57 yr.
No cardiac failure	36 (32%)	11 (38%)	47 (34%)	49 yr.
Mortality rate	23 (21%)	7 (24%)	30 (21%)	

The presence of cardiac insufficiency was of great significance in the outcome of an attack of coronary thrombosis. The mortality rate in the group with heart failure was 30 per cent and in that without it only 4 per cent (Table III), a difference to be attributed almost entirely to the cases with combined left and right ventricular failure; the mortality rate in left ventricular failure alone was the same as that in cases without cardiac insufficiency. Furthermore, failure of both ventricles was present in all but three of our fatal cases.

TABLE III

HEART FAILURE AND MORTALITY RATE

	CASES	DEATHS	MORTALITY RATE
Cardiac failure	93	28	30%
Left only	26	1	4%
Left and right	67	27	40%
No cardiac failure	47	2	4%
Total	140	30	21%

EXACT MEASUREMENTS OF THE CIRCULATION

In studying the dynamics of the circulation several quantitative methods have been evolved. The vital capacity of the lungs was determined almost a century ago by Hutchinson.[18] In our experience it has been very useful, and we are in full accord with White and McGinn[16] when they say that it has too long been neglected. This test consists of measuring the volume of air expelled by a forced expiration following a deep inspiration. The normal for the male averages 4,000 c.c. and for the female 3,500 c.c., varying with the surface area. In the absence of pulmonary disease a reduction in vital capacity is an accurate measure of left ventricular failure, particularly when it is below 60 per cent of normal, as Peabody and his associates[19] and Pratt[20] have demonstrated. In heart disease a diminished vital capacity results from congestion of the lung secondary to insufficiency of the left ventricle. The dilated alveolar capillaries and the transudate in the alveoli encroach upon the alveolar spaces and reduce the capacity and elasticity of the lungs.

The function of the left ventricle may also be tested by the time consumed in the passage of a substance from an antecubital vein through the lungs to the peripheral arteries. Numerous substances have been employed[15, 21, 22] to determine this circulation time. As advocated by Fishberg, Hitzig and King,[23] we have used saccharin, the end point being a sweet taste. The normal time consumed is from 12 to 16 seconds and therefore we have considered 18 seconds or more as indicative of a significant slowing of the circulation through the lungs.

Similarly, insufficiency of the right ventricle can be determined by measuring the arm-to-lung circulation time. Blumgart[21] used radium seed emanation, and Hitzig[24] and Miller[25] suggested ether for this purpose. The normal circulation time is from 4 to 8 seconds and this is prolonged when there is slowing of the peripheral venous return through the right ventricle to the lungs.

Elevation of the venous pressure as evidenced by distended neck veins has been recognized for many years as a sign of cardiac insufficiency. Direct measurement of the venous pressure in an antecubital vein has now become a common procedure in heart failure,[26, 27] but only recently has its importance as an indication of failure primarily of the right ventricle been appreciated. Fishberg and his coworkers[2] stressed the value of this test in the study of heart failure in coronary thrombosis. We have used the direct method of Taylor, Thomas, and Schleiter[28] and have considered a pressure of 9 cm. or higher abnormal.

The arm-to-tongue circulation time was determined in 65 cases (Table IV). In 60 cases it was an accurate index of the severity of failure of the left ventricle, and consequently of pulmonary engorgement. In 5 cases with evidence of left or combined failure, such as râles, enlarged liver, low vital capacity, it was normal. This has been noted also in occasional cases by Robb and Weiss,[15] and Hitzig, King and Fishberg.[29]

TABLE IV

ARM-TO-TONGUE CIRCULATION TIME IN 65 ATTACKS

	NORMAL (12-17 SEC.)	SLIGHTLY PROLONGED (12-20 SEC.)	DEFINITELY PROLONGED (21-30 SEC.)	MARKEDLY PROLONGED (31-60 SEC.)
No. of cases	16	12	26	11
Cardiac failure	5 (31%)	8 (67%)	25 (96%)	11 (100%)
Left only	1 (6%)	3 (25%)	8 (31%)	2 (18%)
Left and right	4 (25%)	5 (42%)	17 (65%)	9 (82%)
Vital capacity—				
Average	2,350	2,600	1,900	1,600
50% of normal or less	25%	16%	54%	73%
Orthopnea	0	2 (16%)	16 (61%)	9 (82%)
Mortality rate	0	1 (8%)	6 (23%)	2 (18%)

The circulation time was definitely prolonged, that is, 21 seconds or more, in 57 per cent of the cases. Clinical signs of cardiac insufficiency, usually of both ventricles, were present in all but one of these cases

and a significantly reduced vital capacity (50 per cent of normal or less) and orthopnea were observed in the great majority. The seriousness of a prolonged circulation time was further reflected in an elevated mortality rate.

The arm-to-lung circulation time measured 9 seconds or more in one-third of the cases studied (Table V). In most of these there were clinical signs of failure of both ventricles, including elevated venous pressure. Two cases in which the ether time was slightly prolonged (9 to 10 seconds) offered no other evidence of cardiac insufficiency, and in the absence of other clinical signs it cannot be stated definitely that this prolongation was a manifestation of heart failure.

TABLE V

ARM-TO-LUNG CIRCULATION TIME IN 40 ATTACKS

	8 SEC. OR LESS	9 SEC. OR MORE
No. of cases	27	13
Cardiac failure	15 (56%)	11 (85%)
Left only	9 (33%)	1 (8%)
Left and right	6 (23%)	10 (77%)
Vital capacity		
50% of normal or less	60%	50%
Venous pressure 9 cm. or more	8%	67%
Arm-to-tongue time 21 sec. or more	37%	85%
Mortality rate	1 (3.5%)	2 (15%)

In most of the cases of isolated failure of the left ventricle the arm-to-lung time was normal. Of 27 patients in whom this measurement was normal, nine were suffering from isolated left ventricular failure accompanied by low vital capacity and prolonged arm-to-tongue time. However, although the prolongation of the arm-to-lung time depends solely on insufficiency of the right ventricle, it was found to be normal in 6 cases with definite right ventricular failure. In two of these the venous pressure was elevated. It seems, therefore, that right heart failure is late in affecting the arm-to-lung circulation time, and, when prolongation does appear, other evidence of failure is already present.

The venous pressure was measured in 84 cases (Table VI). Of the 39 patients in whom it was 9 cm. or higher, only one failed to show

TABLE VI

VENOUS PRESSURE IN 84 ATTACKS

	8 CM. OR LESS	9 CM. OR MORE
No. of cases	45	39
Cardiac failure	31 (69%)	37 (95%)
Left only	19 (43%)	1 (2.5%)
Left and right	12 (26%)	36 (92%)
Vital capacity		
50% of normal or less	32%	59%
Arm-to-tongue time 21 sec. or more	45%	73%
Arm-to-lung time 9 sec. or more	17%	77%
Mortality rate	4 (9%)	12 (31%)

evidence of right as well as left ventricular failure. The arm-to-tongue and arm-to-lung circulation times were prolonged, and the vital capacity was significantly reduced in most of this group. When the venous pressure was found to be elevated, congestion in the lungs and enlargement of the liver had already occurred. Hence an elevated venous pressure appeared only when failure of the right ventricle followed that of the left; it was practically always normal in the presence of isolated left ventricular failure. Blumgart and Weiss[30] also found that elevation of the venous pressure was usually preceded by a decrease in vital capacity and slowing of the pulmonary circulation.

Like the arm-to-lung time, the venous pressure was normal in one-quarter of the patients with clinical signs of combined left and right ventricular failure. Thus in early combined failure the venous pressure may be normal despite a diminished vital capacity, prolonged arm-to-tongue, and in some cases prolonged arm-to-lung circulation times. On the other hand, the presence of a normal venous pressure in some of these cases of left and right failure may be explained by the concomitant presence of shock in which the venous pressure tends to be low.[2]

In this connection the relation of venous pressure to shock was studied. It was lowered to 3 cm. or less in 15 cases, yet clinical signs of shock existed in only half of these. Conversely, the venous pressure was elevated to 9 cm. or more in almost half the patients who were in shock and occasionally to 20 cm. or more. Since congestive heart failure was present in many of the latter group, it appears that the height of venous pressure is determined by the predominance of either shock or congestive failure. No such clear-cut correlation between venous pressure and shock as was reported by Fishberg and his coworkers[2] was found in our series, nor could we confirm their impression of a definite relationship between venous pressure and infarction of the interventricular septum. In necropsy examination of 16 cases, most of them with gross infarction of the septum, the venous pressure measured 12 cm. or above in only five, the highest being 18 cm. In general, there was no correlation between the degree of septal involvement and the height of the venous pressure; in one case with practically complete infarction of the septum and almost no signs of shock the venous pressure was only 8 cm.

The vital capacity proved to be the most accurate measure of the degree of cardiac insufficiency (Table VII). It proved to be accurate not only as a diagnostic sign, but as a prognostic one as well, as Ernstene has reported.[31] Only twelve patients had a vital capacity of 75 per cent of normal or higher; none of these died; and only one had evidence of slight failure of the left ventricle. Almost all the patients with a vital capacity of from 25 to 50 per cent of normal had cardiac insufficiency, and the majority were orthopneic. Of eight patients with a vital capacity of from 15 to 25 per cent of normal,

all had severe left and right failure, six had orthopnea, and two died. In more than two-fifths of the patients the vital capacity measured between 50 and 75 per cent of normal (average 2,500 c.c.). Nearly three-fourths of these had signs of congestive failure, and one-third were orthopneic. It seems, therefore, that even this moderate reduction in vital capacity may be an indication of heart failure.[19] As a rule, the vital capacity increased as the clinical condition grew better and therefore was useful in following the improvement of the patient, particularly when frank clinical signs of passive congestion were absent.

TABLE VII

VITAL CAPACITY IN 80 ATTACKS

	VITAL CAPACITY—PER CENT OF NORMAL			
	76 TO 90%	51 TO 75%	26 TO 50%	15 TO 25%
Vital capacity—				
Average	3,500 c.c.	2,500 c.c.	1,650 c.c.	775 c.c.
Range	2,800 to 4,200	1,600 to 3,100	1,200 to 2,000	400 to 1,100
Incidence in 80 attacks	12 (15%)	35 (44%)	25 (31%)	8 (10%)
Cardiac failure	1 (8%)	26 (73%)	21 (84%)	8 (100%)
Left only	0	11 (31%)	6 (24%)	2 (25%)
Left and right	1 (8%)	15 (42%)	15 (60%)	6 (75%)
Orthopnea	1 (8%)	11 (31%)	16 (62%)	6 (75%)
Circulation time				
Prolonged 21 sec. or more	1 (11%)	10 (38%)	15 (75%)	6 (86%)
Slightly prolonged 18-20 sec.	3 (33%)	6 (23%)	2 (10%)	0
Normal 12-17 sec.	5 (55%)	10 (38%)	3 (15%)	1 (14%)
Mortality rate	0	4 (11%)	3 (12%)	2 (25%)

In general, there was a definite correlation between vital capacity and arm-to-tongue circulation time. The latter was prolonged to 21 seconds or more in the majority of cases with a vital capacity less than 50 per cent of normal and in only one case with a normal vital capacity. On the other hand, a normal circulation time occurred in four patients with definite cardiac insufficiency and very low vital capacity. Hence, as Robb and Weiss[15] also found, the vital capacity is usually lowered before slowing of the blood flow and is therefore the first sign of left heart failure. As pulmonary congestion increases, the pulmonary blood flow is slowed and the arm-to-tongue circulation is prolonged. As the strain falls on the right ventricle, the venous pressure is elevated and finally as the peripheral flow is slowed the arm-to-lung time is increased.

PULSE RATE IN CARDIAC INSUFFICIENCY

Clinicians early realized the importance of the pulse rate in estimating the degree of heart failure; a fast rate was associated with cardiac strain and a normal or only slightly elevated rate was a good prognostic sign. Physiologists showed that the rapid rate of heartbeat indicated a mechanically inefficient heart muscle, with increased oxygen

consumption for the work performed.[32-34] When the rate is slow, diastole is long enough for the myocardium to receive sufficient oxygen, and the oxygen consumption per unit of time is the most economical. The mechanism for the increased heart rate in severe heart failure may be explained by the Bainbridge reflex,[35] that is, an increased venous pressure such as occurs in heart failure distends the right auricle and reflexly produces an acceleration in heart rate. Fishberg[17] reasoned that in coronary artery thrombosis reflexes initiated in the carotid sinus and aorta by the drop in blood pressure gave rise to tachycardia.

We also found that the incidence of cardiac insufficiency rose with an increasing heart rate (Table VIII). If at any time in the course of the attack, the rate rose to 120 beats per minute or more, cardiac insufficiency was usually present (85 per cent). When the rate was 100 to 120, cardiac insufficiency was present in three-quarters of the cases. In both these groups the cardiac insufficiency in the majority of the cases was combined left and right ventricular failure. When the heart rate was below 100, heart failure was present in only one-half of the cases. These findings were consistent in heart rates occurring at any time during the attack. Even in the presence of shock a heart rate above 100 usually indicated that there was also cardiac insufficiency.

TABLE VIII

PULSE RATE AND HEART FAILURE (135 ATTACKS)

	60-80	80-100	100-120	120/MIN. OR OVER
No. of cases	16	43	42	34
Cardiac failure	7 (44%)	26 (60%)	30 (71%)	29 (85%)
Left only	3 (19%)	11 (26%)	6 (14%)	6 (17%)
Left and right	4 (25%)	15 (34%)	24 (57%)	23 (68%)
Gallop rhythm	2 (12%)	13 (30%)	16 (38%)	23 (68%)
Mortality rate	1 (6%)	5 (12%)	9 (21%)	15 (44%)

The vital capacity was decreased to 50 per cent of the normal in more than one-half of the cases with tachycardia but in only one-third of the cases with a pulse rate below 100. Gallop rhythm frequently accompanied tachycardia, occurring in almost three-quarters of the patients with a rate of 120 or more, in one-third when the rate was from 100 to 120, and in one-fifth when it was below 100. As Levine[6] and Bramwell[36] have already found, it is uncommon with a slow pulse rate.

The mortality rate was highest in the group with the most rapid pulse rate. When the rate was 120 or more, death occurred in 44 per cent, but in only 10 per cent when it was below 100. In 16 patients the pulse rate never rose above 80, and only one of these died. Therefore, in coronary artery thrombosis tachycardia indicates severe heart failure.

PULSE PRESSURE AND CARDIAC INSUFFICIENCY

A drop in both systolic and diastolic blood pressure usually succeeded coronary occlusion. In many of the cases the drop in the systolic pressure was much greater than that in the diastolic so that the pulse pressure became small. This decrease in pulse pressure has been attributed to the lowered cardiac output resulting from shock. Although it is commonly considered that a pulse pressure of less than 40 mm. is abnormal, it must be remembered that a "normal" pulse pressure depends on the absolute values of the systolic and diastolic pressures. Thus a low pulse pressure is probably more significant when the diastolic pressure is high than when it is normal. Actually we have found that in patients suffering from coronary thrombosis the pulse pressure change was significant only when it fell to 20 mm. or less (Table IX). This occurred in 12 patients, 10 of whom developed cardiac insufficiency, all but one having both left and right ventricular failure. Seven of the twelve patients died, making the high mortality rate of 58 per cent. On the other hand, the incidence of cardiac insufficiency and the mortality rate in the patients with a pulse pressure above 20 mm. corresponded with those for the entire series. It is apparent, therefore, that the incidence of cardiac insufficiency and the mortality rate were increased only when the pulse pressure fell to 20 mm. or less. Coombs[37] reported similar results with a pulse pressure of 25 mm. or less.

TABLE IX

PULSE PRESSURE IN HEART FAILURE (136 ATTACKS)

	31 MM. OR MORE	21 TO 30 MM.	20 MM. OR LESS
No. of cases	73	51	12
Cardiac failure	47 (64%)	34 (67%)	10 (83%)
Left only	17 (23%)	8 (16%)	2 (16%)
Left and right	30 (41%)	26 (51%)	8 (67%)
Shock	25 (34%)	23 (45%)	9 (75%)
Mortality rate	10 (14%)	9 (18%)	7 (58%)

The effect of shock or peripheral circulatory failure on pulse pressure is shown by the presence of this condition in three-fourths of the patients with a pulse pressure of 20 mm. or less and in only one-third of the patients with pulse pressure above 30 mm. The high mortality in the former group is probably the result of a combination of severe peripheral and congestive heart failure.

HEART SOUNDS

A change in the intensity and quality of the heart sounds following coronary occlusion has long been noted and is of great diagnostic value. The first sound becomes muffled or faint, and therefore the second seems relatively louder. The two sounds may be of equal intensity (tic-tac),

and if the rate is rapid, embryocardia results. A definite decrease in intensity occurs usually within two or three days following the attack but occasionally may not be observed for two weeks.

Although the classification of heart sounds according to quality is a subjective one, pertinent observations have resulted from a study of this type (Table X). In ninety-one patients considered to have faint or poor heart sounds, cardiac failure was present in four-fifths, and the mortality rate was 29 per cent. This contrasted with a death rate of only 9 per cent in those with fair heart sounds. An embryocardia was present in fifteen instances and was practically always associated with shock and tachycardia.

TABLE X

HEART SOUNDS IN 140 ATTACKS

	FAIR SOUNDS	POOR SOUNDS	EMBRYOCARDIA	NO GALLOP	GALLOP RHYTHM
No. of cases	45	91	15	96	54
Cardiac failure	21 (47%)	71 (78%)	9 (60%)	47 (49%)	46 (85%)
Left only	8 (18%)	17 (19%)	2 (13%)	12 (13%)	14 (26%)
Left and right	13 (29%)	54 (59%)	7 (47%)	35 (36%)	32 (59%)
Tachycardia 100 or more	20 (44%)	56 (62%)	13 (87%)	37 (38%)	39 (72%)
Shock	12 (26%)	37 (41%)	13 (87%)	31 (32%)	30 (55%)
Mortality rate	4 (9%)	26 (29%)	2 (13%)	12 (13%)	18 (33%)

Parsonnet and Hyman,[38] recording the heart sounds in fourteen cases of coronary thrombosis with poor heart sounds, found that the first sound had lost its larger amplitude and that the second sound had assumed the usual characteristics of the first. We have recently taken heart-sound records of five patients with coronary thrombosis and have found that in four of these the muffling of the first sound was caused by a loss of high frequency vibrations. Apparently injury to the heart muscle lessens the ability to produce this high frequency vibration because of either a loss of muscle tone or change in intraventricular pressure.

An overacting type of heart sound was occasionally observed; when this was present, another thrombosis or heart failure was found to be imminent. If either of these occurred, the heart sounds became poor.

GALLOP RHYTHM

Diastolic gallop rhythm is an adventitious sound which is heard during diastole of the heart and together with the normal physiological heart sounds gives a definite rhythm like the gallop of a horse.[36, 39] The rhythm usually consists of three distinct sounds, occasionally of four. For years numerous authors have emphasized the significance of this rhythm as a sign of cardiac weakness and failure especially of the left ventricle.[36, 40, 41] Thompson and Levine[42] have recently shown it to be a serious prognostic sign in coronary thrombosis.

In our series diastolic gallop rhythm was present in 54 cases (32 per cent) (Tables X and XI). It was most common when the heart rate was rapid and rarely occurred when the rate was below 80 per minute. White and McGinn[16] reported a similar incidence in heart failure following long-standing hypertension or coronary thrombosis. In our patients gallop rhythm was probably associated with insufficiency of the left ventricle since it was as frequent in those with isolated left ventricular failure as in those with combined left and right ventricular failure. About one-half of the patients in each group developed this sign. The serious prognostic import was borne out by the higher mortality rate (38 per cent) in those patients who presented this finding than in those who did not (13 per cent). Furthermore it was present in the great majority of fatal cases.

TABLE XI

SIGNIFICANCE OF GALLOP RHYTHM IN HEART FAILURE

	CASES	GALLOP RHYTHM	NO. MORTALITY	NO GALLOP RHYTHM	NO. MORTALITY
Cardiac failure	93	47 (51%)	18 (38%)	46 (49%)	12 (26%)
Left only	26	14 (54%)	1 (7%)	12 (46%)	0
Left and right	67	33 (49%)	17 (52%)	34 (51%)	10 (29%)
No cardiac failure	47	7 (15%)	0	40 (85%)	2 (5%)

It is interesting to note that seven of the 54 patients with diastolic gallop rhythm developed no other sign of congestive heart failure and, in fact, had a normal venous pressure, circulation time and relatively high vital capacity. A gallop rhythm may thus be the only sign of myocardial strain following coronary occlusion.

ARRHYTHMIAS

The frequent occurrence of arrhythmias in coronary artery thrombosis has often been commented upon. Not uncommonly they are the first indication of trouble. In our series 19 patients, or one in seven, developed a cardiac irregularity other than extrasystoles. In each of three cases several types of arrhythmia occurred at different periods. Nearly every variety of irregularity was encountered. Excluding premature beats the most common was auricular fibrillation, which was present nine times; auricular tachycardia and heart-block were each present three times, nodal rhythm twice, and auricular flutter once. Finally, ventricular tachycardia, emphasized by most authors, occurred only once and lasted but a short time. Premature beats were observed in 25 patients. It is interesting that they were ventricular in origin in three-fourths of the cases, presumably because the infarction affects the ventricle primarily.

In most cases the arrhythmias appeared soon after the thrombosis had taken place, but occasionally auricular tachycardia and fibrillation set in after two or three weeks. The onset was often accompanied

by collapse, especially in cases with sudden marked increase in heart rate as in auricular fibrillation or tachycardia. The outstanding feature of these arrhythmias was the fact that they usually disappeared spontaneously after a short period and in some instances were only fleeting. This was particularly true in auricular fibrillation, as previously reported.[43] Only twice did an arrhythmia become permanent, in one patient with auricular fibrillation who received digitalis and in another with incomplete heart-block.

The transitory nature of the arrhythmias may be explained in several ways. The majority seem to arise either reflexly from the functional derangement attendant on the acute injury to the heart or directly from an irritable focus in the damaged area. Second, in coronary thrombosis a strain is placed on the auricles[1] which may account for the initiation of auricular flutter or fibrillation. The right auricle may be the site of damage in thrombosis of the right coronary artery, and this may initiate auricular fibrillation, flutter, tachycardia, or nodal rhythm. However, there were cases with left coronary occlusion which developed these arrhythmias too. Finally, the conduction system may be the site of injury, particularly in thrombosis of the right coronary artery which supplies the S-A and A-V nodes and the posterior part of the intraventricular septum. Campbell[44] has reported two cases in which stenosis of the specific artery to the A-V node or bundle produced no change in rhythm during life. Usually normal rhythm is reestablished as soon as the initial shock has disappeared and the heart has adjusted itself, but even when there is actual damage of the conduction system as in heart-block, the arrhythmia is likely to be transitory because of the profuse anastomosis between the vessels supplying this area.[45] In this case the duration is usually longer.

In our series the arrhythmias did not play an important rôle in the outcome of the attack. Only four of the nineteen patients, three with auricular fibrillation and one with complete heart-block, died during the period of irregularity. Collapse and heart failure which were also present probably were aggravated or induced by the arrhythmia. Most of the remaining fifteen cases presented some degree of heart failure. This was severe and associated with collapse only when the cardiac rate was either very rapid as in paroxysmal tachycardia, or very slow as in complete heart-block. The importance of the heart rate is illustrated in another way by two cases. Each of these patients had suffered a coronary occlusion a short time previously. Both were suddenly seized with severe precordial pain and went into collapse; auricular fibrillation with a rapid ventricular rate was present in one case and auricular tachycardia in the other; in both the electrocardiogram showed changes characteristic of coronary thrombosis. They were, therefore, considered to have suffered a second occlusion. However, when the symptoms and the electrocardiographic abnormalities disappeared completely within twenty-four hours of the cessation of

the arrhythmia, it was evident that the entire episode could be accounted for by the effect of a sudden increase in cardiac rate on a heart already damaged by a previous thrombosis.

RESPIRATORY RATE

Peabody, Wentworth, and Barker[19] suggested that in the absence of pulmonary disease the respiratory rate, like the pulse rate, is a useful and simple index of heart failure. These authors have shown that heart failure, by reducing the vital capacity of the lungs, necessitates an increase in pulmonary ventilation to supply the patient with adequate oxygen. With a lowered vital capacity and increased minute volume of respiration, the respiratory rate must be increased. These three factors are chiefly responsible for the dyspnea of heart failure. The diminished vital capacity may not alone be responsible for the increase in number of respirations per minute; pulmonary congestion may cause a reflex acceleration of breathing through the vagus nerve and the respiratory center.[46]

In our cases of coronary thrombosis the respiratory rate remained normal unless cardiac insufficiency or a pulmonary complication, such as pneumonia or infarction, developed (Table XII). In the absence of these complications the rapidity of the respiratory rate indicated, not only the presence, but also the degree of cardiac insufficiency. A rapid respiratory rate was usually found in the first week of the illness. When it was 20 per minute or less, cardiac insufficiency was present in only a small group of cases and was of the left ventricle alone. Orthopnea was absent; the vital capacity was relatively high; and none of the attacks was fatal. As the respiratory rate reached 28, the incidence of combined cardiac insufficiency, orthopnea, and fatal attacks rose, and the vital capacity was diminished. Only four of 35 patients with a respiratory rate over 28 had no cardiac insufficiency, and in these the tachypnea was due to a pulmonary complication.

TABLE XII

RESPIRATORY RATE AND HEART FAILURE (132 ATTACKS)

	20/MIN. OR LESS	21 TO 24	25 TO 28	29 OR MORE
No. of cases	22	44	31	35
Cardiac failure	8 (36%)	27 (61%)	25 (81%)	31 (87%)*
Left only	6 (27%)	7 (16%)	9 (30%)	3 (9%)
Left and right	2 (9%)	20 (45%)	16 (51%)	28 (80%)
Orthopnea	0	15 (34%)	19 (61%)	27 (77%)
Vital capacity				
Per cent of normal	66%	57%	56%	16 (40%)
50% of normal or less	12%	44%	47%	42% 60%
Mortality rate	0	5 (11%)	7 (23%)	

*The other four patients without cardiac insufficiency suffered from bronchial asthma or pneumonia.

DYSPNEA AND ORTHOPNEA

Dyspnea has been described as the initial and cardinal symptom of heart failure[47] and, as we now know, specifically of left ventricular failure. Orthopnea is, of course, an advanced type of dyspnea. Its mechanism is probably due to a reduction in vital capacity and reflex stimulation of the respiratory rate which results in increased pulmonary ventilation, factors that are present in congestion of the lungs. Since a sitting or semirecumbent position relieves the patient, it may be assumed that the orthopnea can be attributed to the increased vital capacity[48, 49] and diminished pulmonary ventilation[19, 46] which occur in this position.

Orthopnea was a frequent symptom in our series, occurring in 44 per cent of the cases (Table XIII). Frequently it was present in the absence of pain. Nearly always present in the more seriously ill patients, it was an implication of severe combined left and right failure. The mortality rate was 43.5 per cent in this group and was only 3 per cent in those without orthopnea. The vital capacity was usually lowered to 50 per cent of normal or less, the average being 1,800 c.c.

TABLE XIII

ORTHOPNEA AND VITAL CAPACITY

	NO.	AVERAGE VITAL CAPACITY		MORTALITY RATE
		C.C.	% OF NORMAL	
Cardiac failure with orthopnea	62 (44%)	1,800	44	27 (43.5%)
Left only	9	1,700	43	1 (11%)
Left and right	53	1,800	44	26 (49%)
Cardiac failure without orthopnea	31 (22%)	2,100	55	1 (3%)
Left only	17	2,000	52	0
Left and right	14	2,300	57	1 (7%)
No cardiac failure or orthopnea	47 (34%)	2,700	66	2 (4%)

On the other hand cardiac insufficiency may occur without orthopnea. Thirty-one patients with evidence of failure of both left and right ventricles were not orthopneic. It is noteworthy that in this group the vital capacity was somewhat higher, averaging 2,100 c.c. and the mortality rate was only 3 per cent. As the patients without signs of cardiac insufficiency had a vital capacity averaging 2,700 c.c., it is evident that orthopnea is associated with a lowered vital capacity secondary to pulmonary congestion and is of serious prognostic import.

PULMONARY EDEMA

As far back as 1878 Welch[9] produced pulmonary edema in rabbits by injuring the left ventricle. Since then, clinical observations have emphasized the relation between pulmonary edema and insufficiency of the left ventricle secondary to acute myocardial infarction.[13, 16, 17, 50, 51] When the ventricle fails, congestion of the lungs appears; if it is severe

or sudden in occurrence, the patients become very dyspneic and develop cardiac asthma. A further increase in congestion results in a sufficiently high pressure in the pulmonary capillaries to bring on actual edema of the lungs. Libman,[52] Levine[6] and Herrick[53] pointed out that pulmonary edema may be the first or only indication of a coronary occlusion and unless characteristic electrocardiographic evidence of myocardial infarction is obtained, such an attack may go unrecognized. Nine of our patients who developed pulmonary edema had little or no precordial pain. Massive pulmonary edema was not infrequent, occurring in twenty patients, or over one-fifth of those with congestive failure (Table XIV). It was more common in women than in men, perhaps because of the higher incidence of previous hypertension in the former.

TABLE XIV

PULMONARY EDEMA IN 140 ATTACKS

	NUMBER
Incidence	20 (14%)
Sex—	
Male	14 (70%)
Female	6 (30%)
Previous occlusion	14 (70%)
Previous hypertension	17 (85%)
Enlarged heart	19 (95%)
Minimal pain	9 (45%)
Left and right heart failure	18 (90%)
Mortality	10 (50%)

An initial attack of coronary thrombosis was seldom complicated by pulmonary edema except in patients with long-standing hypertension. The great majority of these patients gave a history of a previous occlusion as well as hypertension, and all but one had definite cardiac enlargement. In other words, pulmonary edema following coronary occlusion usually occurred in those whose hearts had been subjected to long-standing left ventricular strain. Practically all the patients with pulmonary edema also showed such evidence of failure of the right ventricle as enlarged liver, distended peripheral veins and elevated venous pressure. The mortality rate of 50 per cent, a rate considerably higher than in other patients with congestive failure, was further evidence of the severity of the cardiac failure.

SHOCK

Heart failure following coronary thrombosis differs from ordinary congestive failure in that it is frequently associated with peripheral circulatory collapse. The latter is probably a nervous phenomenon initiated by the acute myocardial injury and results in a low peripheral venous pressure, reduced venous return to the heart, and diminished cardiac output. In congestive heart failure, on the contrary, there is

an increase in venous pressure. The clinical picture of the attack depends therefore on which of the two elements predominates.

In their recent study of myocardial infarction Fishberg and his associates[2] found that in patients with previously normal hearts shock might dominate the picture completely, particularly early in the attack, and that in patients with previous heart failure the signs of either shock or failure might be foremost. The frequent absence of cardiac insufficiency during shock, even when extensive infarction existed, they attributed to the diminished venous return which lessens the work of the heart and prevents passive congestion of the veins. This conclusion is borne out by the low venous pressure and normal circulation time present during the stage of shock. Shock immediately after the attack, followed gradually by signs of passive congestion as the shock diminished, was a sequence frequently found in their patients. We have been less successful in dividing our cases into those with shock and those with heart failure. In most instances we found that the two were present simultaneously, particularly when the patients were observed for several days following the onset of the attack. Harrison,[3] too, points out the frequent association of these conditions following coronary thrombosis.

Manifestations of shock, such as grayish pallor, moist clammy skin, cold extremities, collapse or marked weakness, and rapid fall in blood pressure, appeared in almost one-half our patients (Table XV). Four-fifths of these developed, in addition, passive congestion, either simultaneously or subsequent to recovery from the effects of shock. On the other hand, only three-fifths of those without shock developed cardiac insufficiency. It may be assumed then that both shock and cardiac insufficiency usually occur together and in the more seriously ill patients with large infarctions—a conclusion borne out by the fact that two-fifths of the patients in shock died. As practically all the fatal cases also suffered from a severe degree of congestive failure, it is obvious that both peripheral circulatory and cardiac failure are important factors in determining the outcome of an attack of thrombosis. In the fatal cases, however, the picture of congestive failure usually predominated over that of shock, except when death occurred very early in the attack.

TABLE XV

SHOCK AND HEART FAILURE IN 135 ATTACKS

	NO SHOCK	SHOCK
No. of cases	74	61
Cardiac failure	45 (61%)	50 (81%)
Left only	16 (22%)	10 (17%)
Left and right	29 (39%)	40 (64%)
Cyanosis	37 (62%)	53 (83%)
Mortality rate	5 (7%)	25 (42%)

CYANOSIS

Excluding patients with pulmonary complications, three types of cyanosis were observed. In the stage of shock there was usually a grayish pallor rather than cyanosis. In the majority, the addition of left ventricular failure produced an ashy gray cyanosis due to the admixture of bluish cyanosis and pallor. Many clinicians have noted the characteristic facies which this ashy gray hue imparts to coronary thrombosis. Second, when severe right heart insufficiency was present, the stasis in the peripheral vessels produced the typical dark bluish purple cyanosis seen in ordinary congestive heart failure. Finally, we have recently observed four cases in which an intense, blue, symmetrical acrocyanosis was present in all extremities. These patients were extremely sick and suffered from a combination of severe shock and cardiac failure, with marked slowing of the peripheral blood flow.

Definite cyanosis occurred in 65 per cent of our patients (Table XVI). The incidence of cardiac insufficiency was definitely higher in these than in the noncyanotic patients and furthermore, the incidence of combined left and right heart failure was twice as frequent.

TABLE XVI

CYANOSIS IN 135 ATTACKS

	NO CYANOSIS	CYANOSIS
No. of cases	44	91
Cardiac failure	23 (52%)	68 (75%)
Left only	9 (20%)	14 (15%)
Left and right	14 (32%)	54 (60%)
No cardiac failure	21 (48%)	23 (25%)*
Shock	11 (25%)	53 (58%)
Mortality rate	4 (9%)	26 (29%)

*Nine patients had a pulmonary complication.

Shock developed in more than half of the cyanotic patients, a frequency double that in the noncyanotic patients. The mortality rate was also considerably higher with cyanosis, and conversely nearly all the fatal cases showed a moderate or severe degree of cyanosis. It seems therefore that the type of cyanosis seen in coronary thrombosis is usually a sign of both cardiac insufficiency and shock.

In eleven patients cyanosis of varying degree was observed in the absence of shock, any other sign of cardiac insufficiency, and any pulmonary complication such as pneumonia, pulmonary infarction, or emphysema. It may be that mild temporary shock or cardiac insufficiency occurred very early in the attack before the patients came under observation and that the cyanosis persisted long after these conditions disappeared. Hamman[4] has pointed out that cyanosis may persist throughout convalescence of the attack even after other signs of heart failure have disappeared.

FEVER

Fever is one of the cardinal signs of coronary thrombosis. Although congestive heart failure has been shown to cause fever,[54] it is probable that in coronary thrombosis the fever results from the necrosis of the heart muscle alone. In the absence of infection a rise to 101° F. or more has been taken to indicate the presence of a large area of infarction. Among our 68 patients with such a rise in temperature the incidence of cardiac insufficiency and the mortality rate were considerably higher than in those without fever (Table XVII). Uncomplicated by infection the temperature not infrequently reached 103° F.; it rose to 104° in only seven patients, six of whom were suffering from pneumonia in addition to the cardiac infarction. In the majority of cases fever was highest several days after the onset of the infarction and gradually subsided within the first week. Three-fourths of this group developed cardiac insufficiency. Of nineteen cases with fever for from eight to fourteen days, cardiac insufficiency was present in all but two. Only a minority of patients without fever developed cardiac insufficiency. These observations lead to the conclusion that fever is a reliable guide to the degree of infarction.

TABLE XVII

FEVER AND HEART FAILURE (138 ATTACKS)

	LESS THAN 101° F.	101° F. OR HIGHER
No. of cases	68	70
Cardiac failure	32 (47%)	51 (73%)
Left only	9 (14%)	12 (17%)
Left and right	23 (33%)	39 (56%)
Leucocytosis 15,000 or more	9 (13%)	21 (30%)
Mortality rate	12 (18%)	18 (26%)

Fever of two or three weeks' duration occurred in only three uncomplicated cases; all were in cardiac failure. Three of four patients with fever persisting longer than three weeks developed cardiac insufficiency. However, since all four had a complication other than cardiac infarction to account for the fever, the latter cannot be correlated with the presence of cardiac failure. In ten patients the various complications responsible for prolonged fever were pneumonia, embolic accidents, and renal infection. When fever in coronary thrombosis lasts for more than two weeks, one must search for one of the above or similar conditions, since we have seen that, even when congestive failure is present, fever is ordinarily of short duration.

LEUCOCYTOSIS

Another characteristic sign of coronary thrombosis is leucocytosis. Libman[52] has shown that it may occur within two hours of the attack and begins to disappear usually after two days. The average total white blood cell count is from 12,000 to 15,000, but much higher

figures have been reported. The height of the leucocyte count has been taken as a guide of the extent of myocardial infarction. Recently the prognostic value of the nonfilament and eosinophile percentages has been emphasized.[55]

Although it has been stated that nearly every attack of coronary thrombosis is followed by leucocytosis, the white blood count was less than 10,000 in two-fifths of our patients (Table XVIII). However, the fact must be considered that a number of our patients came under our observation one to two weeks following their attack when the leucocytosis may have subsided. A leucocytosis of 15,000 or more was found in nearly one-fourth of the cases. In these the incidence of cardiac insufficiency was no higher than in the patients with a normal or only a slightly elevated white blood count.

TABLE XVIII

LEUCOCYTE COUNT IN 120 ATTACKS

	LESS THAN 10,000	10,000-14,900	15,000-19,900	20,000 OR MORE
No. of cases	49	43	19	9*
Cardiac failure	32 (65%)	31 (72%)	13 (68%)	6 (67%)
Left only	10 (20%)	7 (16%)	3 (15%)	2 (22%)
Left and right	22 (45%)	24 (56%)	10 (53%)	4 (45%)
Temperature 101° F. or higher.	13 (26%)	26 (60%)	12 (63)%	7 (77%)
Mortality rate	2 (4%)	11 (26%)	6 (31%)	2 (22%)

*Two other patients excluded from this group suffered from an associated lobar pneumonia.

The difficulty of correlating leucocytosis with cardiac failure may be explained in part by the presence of so many other conditions giving rise to leucocytosis, such as pulmonary infection, ventricular mural thrombosis, deep vein phlebitis, and embolization from the latter two sources.

The presence of leucocytosis gives a poor prognosis. The mortality rate of the seventy patients with a white count of 10,000 or more was definitely higher than in those with a normal white count. However, the prognosis was apparently not worse with a count of 20,000 than with one of 10,000. Although there was usually a correlation between leucocytosis and fever, one was present in the absence of the other in a small group of patients.

HYPERTENSION AND CARDIAC ENLARGEMENT

Hypertension has been shown by most writers to be a significant predisposing factor in coronary artery thrombosis, but its relation to heart failure has not been extensively studied. Averbuck[56] found that heart failure in hypertension was usually associated with coronary sclerosis or, less often, with thrombosis. White,[57] too, reported that

in a large series of hypertensive patients coronary thrombosis was not infrequently the factor inciting congestive heart failure. They, as well as numerous other writers,[58-62] found that cardiac enlargement was almost a constant precursor of cardiac failure. Starling and his coworkers[33, 58] established the principle that a heart put under strain compensates by an increase in muscle fiber length and by active stretching of the ventricular wall and therefore a fatigued heart dilates in order to carry on the same circulation and amount of work as a normal heart. When the ventricles are unable to empty themselves completely, dilatation is inevitable and is, as Fishberg[17] has aptly stated, a useful adaptation by the heart to increasing work. Hypertension with its increased arterial resistance induces dilatation which if prolonged is followed eventually by hypertrophy.

Nemet and Gross[61] have shown that in the absence of hypertension muscle damage in chronic coronary disease may lead to cardiac hypertrophy. They accepted the view that increased initial fiber tension, resulting from muscle damage rather than increased work, may be the stimulus to dilatation and hypertrophy, and they emphasized the fact that congestive failure in coronary disease is usually the failure of the hypertrophied heart. In a post-mortem study, Nathanson[59] showed that in the absence of definite cardiac enlargement congestive failure rarely develops in patients with acute or chronic coronary artery disease. The enlarged heart has been shown to be an inefficient heart. Since its oxygen consumption is related to the degree of dilatation,[33, 63] an enlarged dilated heart consumes an increased amount of oxygen and liberates a high quantity of energy but the useful work accomplished is relatively small, and hence the mechanical efficiency is low.

Evidence of hypertension, that is, a systolic blood pressure of 150 mm. or more or a diastolic of 90 mm. or more, was established in 70 per cent of our patients either at the time of observation or from a reliable history (Table XIX). Cardiac insufficiency developed in almost three-quarters of these hypertensive patients, but in only half of those without elevated blood pressure. The presence of hypertension had only slight if any effect on the mortality rate. An analysis of cases with cardiac failure showed a history of antecedent hypertension in only 75 per cent, that is, in one-fourth of the patients failure was apparently not preceded by hypertension.

TABLE XIX

HYPERTENSION AND HEART FAILURE (140 ATTACKS)

	NO HYPERTENSION	HYPERTENSION
No. of cases	43	97
Cardiac failure	23 (53%)	70 (72%)
Left only	4 (9%)	22 (23%)
Left and right	19 (44%)	48 (49%)
Mortality rate	7 (16%)	23 (24%)

A more constant association was found between cardiac enlargement and heart failure than between hypertension and heart failure. A heart was considered enlarged if dullness was increased to the left (midclavicular to anterior axillary line) or to the right (at least 3 cm. to the right of the midsternum) or if the transverse diameter on teleroentgenogram measured more than one-half the total internal thoracic diameter of the chest. By either of these standards, the heart was found definitely enlarged in 65 per cent of the cases (Table XX). Evidence of cardiac insufficiency, usually of both ventricles, was present in nine-tenths of these. Although dilatation theoretically must occur in a normal-sized heart which becomes insufficient, six patients with definite congestive failure showed no clinical evidence of cardiac enlargement. The incidence of cardiac enlargement in the patients who developed congestive failure was much higher, 87 per cent (Table XXI). In nearly all instances the insufficiency was of both the left and right ventricles. Moreover, only one-fifth of the patients who did not develop cardiac insufficiency had an enlarged heart. It may be concluded that patients with coronary thrombosis are much more prone to develop congestive failure when cardiac enlargement is present.

TABLE XX

HEART SIZE AND HEART FAILURE (140 ATTACKS)

	NORMAL	ENLARGED
No. of cases	49	91
Cardiac failure	12 (24%)	81 (89%)
Left only	6 (12%)	20 (21%)
Left and right	6 (12%)	61 (67%)
Mortality rate	0	30 (33%)

TABLE XXI

HEART ENLARGEMENT AND HEART FAILURE

	CASES	ENLARGED HEART
Cardiac failure	93	81 (87%)
Left only	26	20 (77%)
Left and right	67	61 (91%)
No cardiac failure	47	10 (21%)
Total	140	91 (65%)
Fatal attacks	30	30 (100%)

It may be assumed that the existence of cardiac enlargement in the majority of our patients was due primarily to preexisting hypertension since this was present in 85 per cent of those with enlarged hearts and in only 41 per cent of those with normal-sized hearts. Such a high incidence in the former group emphasizes the rôle of hypertension as a factor in cardiac enlargement and helps to explain the greater incidence of cardiac insufficiency in the hypertensive patients.

In a small number of cases the cardiac enlargement observed in a patient with coronary thrombosis may be attributed to the congestive

heart failure. A large infarction occurring in a previously normal-sized heart may produce sufficient myocardial weakness to lead to cardiac dilatation and congestive failure. Observation in such cases may show the heart to enlarge as the signs of passive congestion appear. In a patient under our care for many years, repeated teleroentgenograms showed a normal-sized heart. After an attack of pulmonary edema, initiated by a coronary occlusion, there was a sudden enlargement of the cardiac shadow which has persisted since recovery from the thrombosis.

MULTIPLE ATTACKS

In a large series of cases of coronary thrombosis already reported,[64] a history of one or more previous occlusions was elicited in approximately one-half the patients. Our own observations, as well as those of other authors, attest to the great frequency of multiple attacks.[65-67] In the present group a typical history of a previous attack was obtained in 47 per cent of the patients (Table I). Of these, four-fifths developed congestive failure, the incidence rising with each succeeding attack, that is, from 53 per cent in the initial attack to 88 per cent in the third attack. It is interesting to note that as many as half the patients suffering an initial attack of thrombosis developed failure since some authors[2] have emphasized that this sequence is uncommon. A history of a previous occlusion was obtained in only 12 per cent of the patients who did not develop heart failure.

The mortality rate, like the incidence of cardiac insufficiency, rose with each succeeding attack, being 11 per cent in the initial and 50 per cent in the third attack. Conversely the majority of patients dying of coronary thrombosis have had a previous occlusion as well as cardiac failure. Repeated attacks, then, are attended by increasingly more frequent failure and, consequently, contribute to a poorer prognosis.

LOCATION OF INFARCT

Attempts have been made in the past to localize the site of myocardial infarction by the type of heart failure present. It was thought by some investigators[12, 68, 69, 70] that occlusion of the right coronary artery led to predominately right ventricular failure while occlusion of the left coronary artery was associated with predominately left ventricular failure. Since thrombosis of either the left or the right coronary artery results in infarction of the left ventricle, such an attempt to localize the site of thrombosis seems theoretically unsound, a conclusion borne out by our own data and that of Fishberg and his coworkers.[2] The latter authors found that left ventricular failure or combined left and right ventricular failure resulted from either infarction of the anterior or posterior surface of the left ventricle. They concluded, therefore, that a differentiation of the left and right coronary thrombosis could not be made from the type of heart failure

present. Nevertheless, Libman[68] has observed several cases in which right heart failure, as manifested by a rapidly enlarging liver, appeared a few hours after occlusion of the right coronary artery.

Analysis of the electrocardiograms and post-mortem material in our series (Table XXII) reveals that infarction of the anterior surface of the left ventricle (T_1, Q_1 type) was not much more common than infarction of the posterior surface. The right coronary artery was involved as often as the left. Other authors[2, 71] have made the same observation. The incidence of cardiac failure in both groups was practically the same. Moreover, there was only a slightly higher incidence of right heart failure in posterior than in anterior infarction. As many as one-third of the patients with signs of occlusion of the left anterior descending coronary artery developed manifestations of combined left and right ventricular failure. The mortality was the same for both groups. But when signs of involvement of both surfaces of the left ventricle were present (T_1, T_2, T_3 type), probably due in many cases to occlusion of more than one vessel, both the incidence of cardiac insufficiency, particularly combined left and right failure, and the mortality rate rose considerably.

TABLE XXII

LOCATION OF INFARCT AND HEART FAILURE

	ANTERIOR $T_{1, 2}$	POSTERIOR $T_{2, 3}$	ANTEROPOSTERIOR $T_{1, 2, 3}$
No. of cases	57	48	32
Cardiac failure	34 (60%)	31 (65%)	27 (85%)
Left only	13 (23%)	8 (17%)	5 (16%)
Left and right	21 (37%)	23 (48%)	22 (69%)
Mortality rate	9 (16%)	7 (15%)	11 (34%)

It has been suggested by Libman[72] and Fishberg and his associates[2] that infarction of a large portion of the interventricular septum may lead to predominantly right ventricular failure, with distended neck veins, high venous pressure and engorged liver. In our own series gross septal infarction was found in half the fatal cases that were examined post-mortem. All but one had developed a moderate degree of right ventricular failure. This condition, however, was just as frequent and just as severe in the fatal cases that showed little or no septal infarction. Therefore, no direct correlation between septal infarction and right ventricular failure can be drawn from our present material.

FATAL CASES

Our fatal cases and post-mortem observations yielded instructive information. Of the 140 cases reviewed here, death occurred in 30 and autopsies were performed in 23. With two exceptions these patients had manifestations of moderate to severe cardiac failure, which was in most instances combined left and right ventricular failure (Table

XXIII). The two patients who did not develop congestive failure died suddenly early in the attack, one of a ruptured left ventricle and the other in a convulsion, probably due to a cerebral embolus.

TABLE XXIII

HEART FAILURE IN FATAL ATTACKS

	NONFATAL ATTACKS	FATAL ATTACKS
No. of attacks	110	30
Cardiac failure	65 (59%)	28 (93%)
Left only	25 (24%)	1 (3%)
Left and right	40 (35%)	27 (90%)
No cardiac failure	45 (41%)	2 (7%)*

*Two sudden deaths: (a.) rupture of left ventricle; (b.) convulsive seizure.

Acute thrombosis of the left and right main arteries or their branches occurred with equal frequency, a finding which corroborated our earlier conclusion drawn from the electrocardiographic studies. More than one artery was acutely involved in seven cases; in three of these as many as three arteries had been occluded by recent thrombi. Five of the seven cases also showed evidence of previous occlusions. In seven other cases there was recent occlusion of one artery without evidence of occlusion of any other artery. Four of these were in the left anterior descending or left circumflex and two in the right circumflex artery. Death resulting from a closure limited to only a branch of the right coronary is rare, but the occurrence of two such cases in a series as small as this disproves the contention of some investigators[73] that such a finding is almost never observed at postmortem examination. In these seven cases with a single closure congestive heart failure was absent in two and was not marked in two others.

In view of the fact that recent articles[66] have emphasized that infarction may occur without evident thrombosis and vice versa, it is interesting to report that in one case myomalacia was present, but no evidence of a recent thrombosis was found.

Evidence of previous occlusions was present in fourteen cases. In nearly all, the left anterior descending artery was involved alone or together with the right coronary. Only two cases showed an old occlusion of the right coronary without involvement of the left. It appears then that an initial thrombosis occurs usually in the left anterior descending artery. In the cases in which this could be accurately determined, it was found that the initial occlusion involved this vessel ten times and the right coronary only four times. In the second or third attack the right coronary is more frequently involved than the left. Neither the degree nor type of heart failure depended upon the site of the thrombosis, even when gross infarction of the septum was present. As one might expect, however, the more severe cases proved to have multiple occlusions either old or recent.

We may conclude that in the majority of fatal cases one or two vessels have already been occluded by old thrombosis and that the recent thrombosis frequently involves two or three different large vessels. This explains the tendency to repeated attacks in the same patient and the infrequency in fatal cases of a closure limited to one vessel, an observation made also by Sprague and Orgain[74] and Saphir and his coworkers.[66]

Although coronary thrombosis may occur in a patient with a heart of normal size, practically all the patients examined post-mortem had hypertrophied and dilated hearts. Since all but two of these patients had definite congestive failure, it confirms the conclusion reached earlier that cardiac enlargement is invariably associated with congestive failure.

We have stressed the importance of congestive heart failure in determining the severity and outcome of an attack of coronary thrombosis, but we do not wish to leave the impression that congestive failure was responsible for death in every fatal case. In addition to the congestive failure, severe circulatory collapse played a definite rôle in the fatal issue in seven cases, cerebral vascular accidents in four, pulmonary embolization in three, pneumonia in one, uremia following carcinoma of the bladder in one, and hemopneumothorax following exploration for carcinoma of the stomach in one. However, in those cases, congestive heart failure aided in hastening the fatal outcome.

DIFFERENTIAL DIAGNOSIS

Early recognition of an acute coronary thrombosis is of primary importance. We have found that the patients who succumbed in the first twenty-four to forty-eight hours after admission to the hospital were usually those who had not been told of the seriousness of their condition or in whom the disease was not recognized and who were permitted to walk about or work. It is occasionally very difficult to confirm the diagnosis of coronary thrombosis, but in doubtful cases the patient should be kept in bed until the diagnosis is certain.

We have not infrequently observed the occurrence of coronary artery occlusion even in the presence of marked congestive failure, notwithstanding the impression that such a sequence is rare. Indeed it has been suggested by Luten[75] that many factors in heart failure, such as slowing of the coronary blood flow, may contribute to the onset of coronary thrombosis. At any rate, a sudden increase in the manifestations of heart failure in a patient with chronic coronary disease, even in the absence of precordial pain, should make one suspicious of an acute coronary thrombosis,[7] particularly if the patient has suffered a previous thrombosis. Our post-mortem examinations have stressed this observation. In at least three of our fatal cases with chronic congestive failure, the presence of acute coronary thrombosis, manifested

by rapidly increasing heart failure in the absence of precordial pain or characteristic electrocardiographic changes, was confirmed at autopsy.

We did not find evidence to support the common belief that coronary thrombosis does not occur in patients with auricular fibrillation. Two such cases appeared in our series. It must be remembered, however, that an acute thrombosis may be ushered in with a paroxysm of auricular fibrillation as the only symptom.

The difficulty that often arises in the differentiation of coronary thrombosis from attacks of cholecystitis or other acute abdominal conditions is well known and will not be discussed further here. Serial electrocardiograms may be necessary in the differential diagnosis from pneumonia and pulmonary embolism. The characteristic elevation of the RS-T interval, steadily progressing into an inverted T-wave, is not seen in these conditions. In fact, we believe that only pericarditis with effusion may completely simulate the electrocardiogram of coronary artery thrombosis including the RS-T and T-wave changes. Another differential point is that pulmonary embolism is usually characterized by intense cyanosis and tachypnea out of all proportion to the clinical signs and not relieved by oxygen.

The signs of congestive heart failure should be sought carefully. Although in this investigation we have made use of such aids in diagnosis as determinations of the venous pressure and circulation times, clinical observation alone will be sufficient in the majority of cases. Râles in the lungs and enlargement of the liver are the earliest signs of congestive failure to appear. Occasionally râles in the lungs are absent despite such clear-cut signs of left ventricular failure as low vital capacity and x-ray evidence of pulmonary congestion. This point has been emphasized by Robb and Weiss.[15] We have had the same experience, but we believe that if the patient is regularly and carefully examined râles will rarely be missed when left heart failure is present.

Heart failure in coronary thrombosis is frequently simulated by complicating conditions in the lungs. These may be due directly to the myocardial infarction, as in pulmonary embolism and infarction secondary to mural thrombosis of the right ventricle, or they may be associated conditions such as pneumonia, chronic bronchitis, and emphysema and bronchial asthma. It is in the differential diagnosis that we have found the circulatory measurements, such as the venous pressure and circulation times, most valuable.[76] Although pulmonary disease may be accompanied by dyspnea, orthopnea, cyanosis, low vital capacity, and physical and x-ray signs in the lungs, these circulatory measurements are usually normal. Furthermore, the persistence of fever for more than two weeks should make one suspect that the signs in the lungs may be due to pneumonia and not to congestion. However, the simultaneous presence of both is not uncommon, for the vascular congestion predisposes to infection in the lungs.

We have not infrequently observed moderate azotemia and albuminuria. This does not necessarily indicate primary kidney disease, for congestive failure may also produce these changes. Determining the specific gravity often aids in diagnosis; if it is high, it suggests congestive failure.

A sign of cardiac failure in coronary thrombosis not mentioned heretofore is the appearance of large P-waves in the electrocardiogram. In a recent study Master[1] showed that congestive heart failure was very common following coronary thrombosis, occurring in 36 of his 40 cases and that it was usually associated with large P-waves. The explanation offered was that the injury to the left ventricle or the increased intra-auricular pressure in venous stasis would lead to auricular dilatation. The degree of P-wave enlargement was closely correlated with the degree of congestive failure present.

TREATMENT

Once a diagnosis of coronary artery thrombosis was made, the patient was immediately put to bed. Absolute mental and physical rest was enjoined; this included being fed and avoiding visitors, business cares, and overattention by an anxious family. Enemas and cathartics were not given during the first few days unless distention was severe. The fluid intake was limited to 1,200 c.c. except when azotemia was present. Salt was restricted in cardiac failure.

The patients were underfed the first week, and then, if improvement took place, they were placed on an 800 calorie diet. The diet was adequate and well balanced, consisting of approximately 100 gm. carbohydrate, 50 gm. protein, and 20 gm. fat. Occasionally a Karell diet was given for one or two days a week. This regime of undernutrition eliminates gastrocardiac reflexes, lowers the basal metabolic rate, and diminishes the work of the heart.[77] The systolic and diastolic blood pressure, the pulse pressure, and the heart rate are decreased, indicating a lowering in cardiac output and work of the heart. It is true that the basal metabolic rate is elevated in congestive failure, but it is less high when a diminished caloric intake is used than when the patient is on a regular diet.

We did not use digitalis, for it is usually unnecessary and may actually be harmful. When precordial pain was present, we considered it contraindicated. Levine[6] advocates the use of digitalis when failure complicates coronary artery thrombosis. Very occasionally we have seen digitalis of benefit in severe congestive heart failure in the subacute or chronic phase of the disease, and it may be necessary in the rare cases of auricular fibrillation with rapid ventricular rate in which cardiac failure is impending. We believe, however, that the mercurial diuretics with acidifying drugs like ammonium chloride and ammonium nitrite are usually more efficacious in cardiac failure. Mercupurin has been

given hundreds of times without harmful results even when kidney involvement was a complication. If profuse diuresis occurs, salt must be given to prevent excessive dehydration. The mercurial diuretics together with the acidifying drugs were useful in relieving paroxysmal and nocturnal dyspnea, Cheyne-Stokes breathing and cardiac asthma.[78] Morphine should not be given in conjunction with the mercurial diuretics as it has an antagonistic action.

The xanthine preparations, such as theophyllin and ethylenediamine (aminophyllin), occasionally gave good results when administered intravenously. We observed no definite effect when they were given by mouth. Morphine, or better, dilaudid (Bilhuber-Knoll) has been found an invaluable aid in pain, restlessness, sleeplessness, dyspnea, orthopnea, and cardiac asthma.[64] We prefer dilaudid since it is not so constipating as morphine or codeine.

Some years ago it was suggested[79] that quinidine sulphate be given prophylactically in coronary thrombosis to prevent ventricular tachycardia. Although the authors believed the drug aided in stopping the tachycardia, seven of their eight patients died, an unusually high mortality rate. We object to the use of this drug in myocardial infarction. First, it is unnecessary, for the arrhythmias, particularly the paroxysmal tachycardias, are usually transitory and remit without treatment. Second, we consider quinidine sulphate a dangerous drug; it is a protoplasmic poison. It may stop an arrhythmia, but it may cause more harm by direct action on the cardiac muscle.

We gave glucose intravenously to very few patients since with the regime of undernutrition in the early days following the coronary thrombosis additional food was not required. Even if nausea or vomiting is present, it is unnecessary to resort to intravenous injection because these symptoms last only a day or two. We feel that the benefit derived from the use of glucose intravenously simply to maintain a high glycogen content of the heart muscle is largely theoretical and that in left ventricular failure other measures, such as the use of morphine and the mercurial diuretics, are more efficacious.

Venesection is indicated in pulmonary edema and, perhaps, when there is markedly increased venous pressure with engorged veins, large liver, cyanosis, and high blood pressure. As in other forms of severe congestive failure venesection at times will produce remarkable temporary improvement.

Oxygen therapy was helpful as it occasionally relieved severe pain and was of benefit in cyanosis, marked dyspnea, and pulmonary edema. As ordinarily used, however, an oxygen tent may be uncomfortable and do more harm than good. The moisture should be adequate and excessive cold avoided.

SUMMARY AND CONCLUSIONS

Congestive heart failure occurred in 66 per cent of patients with acute coronary thrombosis. It usually consisted of failure of both ventricles, occasionally of the left ventricle alone.

The mortality rate was 30 per cent in the presence of heart failure and only 4 per cent when it was absent.

The incidence of heart failure and the mortality rate were the same in both sexes. The average age of patients with heart failure was fifty-seven years; of those without it forty-nine years.

The measurements utilized for determining the degree of heart failure were the vital capacity, venous pressure and arm-to-tongue and arm-to-lung circulation times. The vital capacity proved to be the simplest and the most reliable gauge of pulmonary engorgement in failure of the left ventricle.

The following clinical signs were associated with heart failure and with a poor prognosis: pulse rate of 100 or more, pulse pressure of 20 mm. or less, "muffled" or "tic-tac" heart sounds, diastolic gallop rhythm, respiratory rate of 28 or more, cyanosis, orthopnea, pulmonary edema, fever above 101° F. and severe shock. Pulmonary edema at times was the only sign of coronary thrombosis. In cases with shock very profound acrocyanosis might be present.

Arrhythmias of all types were observed. Usually they were transient, disappeared spontaneously and did not alter the prognosis.

Heart failure was more common in patients with a history of a previous occlusion or long-standing hypertension and in those with enlarged hearts. The relation between cardiac enlargement and heart failure is discussed.

Pulmonary complications such as infarction and pneumonia were frequent. The differential diagnosis from heart failure is discussed.

Heart failure was severe when the area of myomalacia was large and when both anterior and posterior surfaces were damaged. However, no correlation was found between the incidence, type, and degree of heart failure and the site of infarction.

Analysis of the fatal cases revealed both heart failure and cardiac enlargement to be almost constant findings. At post-mortem examination it was found that old thrombosis in addition to the acute occlusion was present in the majority of cases, that the left anterior descending branch of the left coronary was usually the initial vessel occluded, that thrombosis was rarely limited to one vessel, and that the incidence of anterior and posterior infarction was about equal.

Treatment consisted of prolonged bed rest, low calorie diet, morphine, mercurial diuretics, oxygen for dyspnea and cyanosis, and venesection if pulmonary edema was present. Digitalis and quinidine were considered unnecessary and even harmful.

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TRIGONOIDATION OF THE SEMILUNAR VALVES AND ITS RELATIONSHIP TO CERTAIN BASAL SYSTOLIC MURMURS

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ALTHOUGH Laennec first published the results of his experiments with the stethoscope as long ago as 1819, and although the great clinicians of at least the latter half of the nineteenth century were fully aware of the necessity of distinguishing between organic and so-called functional heart murmurs, yet, even today, there are physicians to whom the term "functional" murmur represents an entity of suspicious vagueness. Sir James MacKenzie[1] accounted for this state of mind several decades ago when he wrote the following in his famous monograph on diseases of the heart: "As a general rule, the more obtrusive a symptom is, the more it impresses the mind of the observer, and much more importance is attached to it than to less conspicuous phenomena. This is particularly noticeable in signs which are detected by auscultation. To the human mind, sounds arising from obscure causes have always been a source of mystery, and the human imagination, when dealing with the mysterious, invariably associates it with something malign." The physician is perhaps justified in adopting this method of rationalization because of his inherent caution against diagnosing a harmless condition when a serious one may really be present. However, it is equally as serious, if not more so, to diagnose an organic condition when the cause of the misleading evidence is of trifling importance.

In order to eradicate the poor rationalization and the occasional tragic diagnoses sometimes prompted by the discovery of certain systolic murmurs, it is necessary to remove the obscurity surrounding the etiology of these sounds. This can be done only by ascribing the murmur to a definite and plausible physical origin. It is simple logic that such a definite physical phenomenon as a murmur must have a cause that is equally definite whether the murmur is organic or "functional." If the cause can be shown to be physiological, the harmlessness of the murmur is evident and can be readily explained to the patient; if it can be shown to be variable, the variability of the murmur can be explained; if it can be shown to be something other than intrinsic valvular or myocardial disease, a clearer concept of the actually responsible factors is stimulated. Finally, if the cause is definitely known, the physician's self-assurance and diagnostic discrimination are increased.

The classification of obscure systolic murmurs has always been admittedly unsatisfactory. Such terms as "physiological," "accidental," "functional," "important," and "unimportant," have only added to the general vagueness and have often been wrong in their interpretation. Thus the murmur that accompanies hypertension or syphilitic aortitis with normal aortic valves may be termed "functional" as far as the valves themselves are concerned, but the term does not take into account the serious organic disease that makes this "functional" murmur possible. Again, the common pulmonary systolic "functional" murmurs may be harmlessly physiological, or they may represent serious organic lung disease. An attempt will not be made here to classify these murmurs. Suffice it to say that the murmurs to be considered are those which occur in the presence of valves which, if they could be examined, would be pronounced intrinsically perfectly normal. The problem to be settled is how such valves can give rise to murmurs and what the conditions are which enable them to do so. The study of this problem may be initiated by considering the systolic murmurs produced at the pulmonary orifice in the presence of intrinsically normal valves.

Systolic murmurs are extremely common over the pulmonary area —Balfour's area of auscultatory romance—yet it is known that structural disease of the pulmonary valves is very rare. So common is this murmur that in the great majority of cases, it must of necessity be regarded as a normal physiological phenomenon. In a smaller group of cases it is due to the effects of excessive metabolic and nervous activity on the heart, and in a few cases it is due to extracardial disease, especially of the lungs. Robinson[2] states: "The soft systolic murmur so frequently heard at the base in healthy individuals, especially during youth, offers an interesting field for speculation. . . . . The pulmonary orifice seems to be especially the one at which vibrations are apt to be set up by the passage of the blood when no structural change in the tissues has taken place."

When we examine the various conditions in which a nonorganic pulmonary systolic murmur may be found, we find that they are all associated with a common factor, viz., overfilling or distention of the pulmonary artery. The occurrence of such a common factor suggests that it is this state of dilatation which is fundamentally responsible for the production of the pulmonary systolic murmur associated with normal valves, and it is believed that the true physical explanation for the murmur can be and has been satisfactorily demonstrated on this basis. Years ago, Austin Flint suggested that the pulmonary systolic murmur was due to a dilatation of the conus arteriosus, but, so far as the writer knows, a physical explanation as to why such dilatation should cause a murmur has never been given.

Let us here briefly note a few anatomical facts in regard to the conus and pulmonary artery. It is a commonly held idea that the conus is separated from the artery itself by a junctional ring of fibrous tissue which supposedly is fairly efficient in preventing dilatation of the pulmonary orifice. If one will take the trouble to look for this ring both macroscopically and microscopically, it will be found to be a greatly overrated and practically nonexistent structure in the human heart. In other words, for all practical purposes, there is no such thing as a pulmonary "ring."

The ends of the free margins of each semilunar valve pocket are attached to the wall of the pulmonary artery itself at some distance above the junction of artery and conus. They are not attached to a fibrous ring. The attachment of the free margins to the wall of the artery is effected through the intermediation of three fibrous nodules, each of which serves as a common point of attachment for the adjacent ends of two cusp margins. Examination will disclose the fact that these fibrous nodules do not stretch when the artery itself is stretched or dilated, and that therefore the adjacent ends of the cusp margins do not pull away from each other when the vessel dilates. The deeper portions of each valve pocket are attached to the endocardium covering the conus.

The pulmonary artery itself is quite a soft, relatively thin, very easily dilatated, and very easily compressed structure. If one places the two index fingers inside the pulmonary orifice and attempts to dilate the latter, it will be found that the first real resistance to stretching is offered by the inelastic valve margins themselves, not by any fibrous ring. If a longitudinal section is made in the pulmonary artery and conus, exactly through one of the common nodules, and the region of the cusps is then transversely stretched, it will be found that stretching is limited by the relatively inelastic valve margins. If each cusp margin is now snipped with the scissors, it will be found that the artery is dilatable for a considerable degree beyond the point at which it was previously limited by the valve edges. With these anatomical facts in mind, we may now consider some of the physical changes which occur at the pulmonary orifice during systole of the ventricles.

If a circle is drawn, say of 1 inch in diameter, or approximately the average diastolic diameter of the pulmonary orifice, and it is divided by three radii into three equal sections of 120 degrees, the diagram may be taken to represent the pulmonary orifice with its valve cusps closed. Now it is a fact that for small circles of this size —and for even much larger ones—the sum of any two of the radii drawn is almost exactly equal in length to the 120 degree segment of circle which they subtend. Thus in the circle given the sum of any two radii is equal to 1 inch, while the segment of the circle which they subtend measures 1.04 inches. It follows from this that, if the valve

opens while the pulmonary artery remains the same size, then each free cusp margin, which is equal to the sum of two radii, will fold back until in almost exact apposition with the wall of the artery. In this position the cusp margin will offer no resistance to the onrush of blood. As a matter of fact, the free margin of each valve cusp is somewhat more than equal to the sum of two radii because of the fact that it extends slightly downward as well as inward toward the central point of the lumen from its mural attachments. This fact enables the margin of the cusp actually to fit back easily against the wall of the undilated artery.

An entirely different relationship results if the pulmonary artery is dilated or becomes dilated at the moment the valve opens, and it is surprising mathematically how little dilatation is necessary to produce this change in relationship. We have seen above that the first appreciable obstruction to wide dilatation of the pulmonary orifice is produced by the unyielding margins of the valve cusps themselves, that the artery itself is dilatable for a considerable distance beyond this

Fig. 1. Fig. 2. Fig. 3.

Figs. 1, 2, and 3.—Successive degrees of dilatation and trigonoidation.

point of resistance, and that the adjacent ends of the cusp margins are attached to common fibrous nodules which do not themselves stretch. Because of these facts, as the artery progressively dilates, the cusp margins fit less and less snugly against the artery wall during systole, as shown successively in Figs. 1, 2, and 3. At a point of maximum dilatation the edges of the cusps would tend to form a triangle within the circle of the artery. It is unlikely that such a true triangle is ever formed, for the onrushing column of blood would cause the margins to bow backward to some degree. Even in well-marked dilatation, Fig. 3 would be a better representation of the relationships than full triangulation.

This tendency of the cusp margins to subtend rather than to fit snugly into each 120 degrees of the pulmonary artery as the latter dilates may be conveniently referred to as "trigonoidation" of the semilunar valves, since the margins arch between their points of attachment to the vessel wall and form the boundaries of a figure which is known in plane geometry as a trigonoid. That such trigonoidation

actually occurs was shown by the following experiment: A heart was obtained at the autopsy of a patient who had died of pulmonary tuberculosis. The inferior vena cava was plugged with a cork and tightly tied around the latter. A cork through which glass tubing passed was similarly used to plug the superior vena cava. A clean, 150 c.c. Erlenmeyer flask was tied by its neck into the pulmonary artery close to the bifurcation. Air was now pumped into the right heart through the glass tubing in the superior vena cava. On looking through the bottom of the Erlenmeyer flask the pulmonary valve margins were seen to become completely triangulated as the conus and artery dilated. Variations in the tension of the valve margins were obviously produced when the right auricle was squeezed and then relaxed, thus varying the pressure and degree of dilatation in the

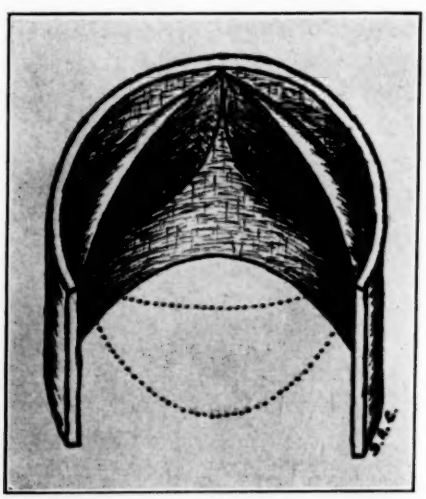

Fig. 4.—Longitudinal section of pulmonary artery through valves, showing trigonoidation.

conus and pulmonary artery. The contrast between the triangulated valve margins and the stretched circumference of the pulmonary artery was striking, there being well-marked sinuses behind the cusps. From the bottom of the Erlenmeyer flask the appearance of the triangulated cusps might be best described as a three-sided funnel within the lumen of the artery.

Trigonoidation of the semilunar valve margins results in ideal conditions for the production of a systolic murmur. It transforms the pulmonary orifice into a structure closely resembling the larynx with its vocal cords, except that here we have three cords instead of two. Figure 4 may be taken to represent a longitudinal section of a pulmonary orifice showing trigonoidation of the valve margins. The taut edges of the somewhat inverted cusps will obviously offer frictional resistance to the moving column of blood and will therefore be

set into vibration. Such a mechanism is so ideal physically for the production of a systolic murmur that, on the basis of trigonoidation, it is no wonder the pulmonary murmur is so common and can be so easily produced. The pulmonary artery dilates considerably, of course, with each systolic stroke of the right ventricle, and the accompanying moderate trigonoidation of the semilunar valves, while perhaps not producing an audible murmur, has an important physiological function. It results in failure of complete obliteration of the valve pocket, and consequently the recoil of the artery following systole immediately distends the valve pockets with blood and thus closes the valve orifice, allowing little or no reflux.

It is to be noted that, while on the average each pulmonary valve cusp occupies 120 degrees of circumference of the pulmonary artery, sometimes one of the cusps is a little larger than the others. This favors the production of a murmur, for any cusp occupying more than 120 degrees, provided that its margin does not exceed the sum

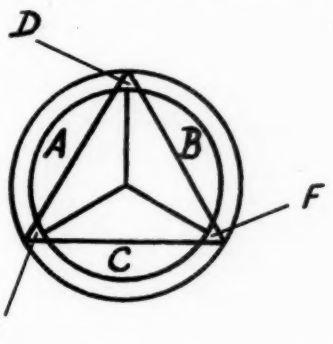

Fig. 5.—Diagram showing the relatively slight dilatation theoretically needed to produce full triangulation of the cusp margins. Each side of the triangle is equal to the sum of two radii of the smaller circle. Actually, more dilatation than here shown is needed to produce full triangulation.

of two radii, will have increased difficulty in folding its margin back to the vessel wall. This was well shown in the above experiment in which one of the cusps occupied slightly more than 120 degrees. Such a relationship accounts for the systolic murmur associated with congenitally bicuspid valves, for in this condition each cusp margin occupies a diameter and subtends 180 degrees.

Figure 5 shows what a relatively slight enlargement in the diameter of a small circle is needed to produce a complete triangulation of the radii. Thus the inner circle, 1 inch in diameter, with the three radii, represents the undilated pulmonary artery with the valves closed, while the outer circle, only about 0.2 inch larger in diameter, shows the valve margins fully triangulated by the moderate dilatation. Actually, more dilatation than this is required to produce triangulation since the cusp margins are slightly longer than two radii.

Figure 5 also demonstrates an important and seemingly paradoxical point, namely, as the pulmonary artery dilates, the area bounded by the cusp margins actually becomes smaller. Thus the combined area of the subtended segments *A*, *B*, and *C* of the undilated artery is lost during dilatation, while the tiny triangles *D*, *E*, and *F* combined represent the area gained. Obviously a great deal more area is lost than is gained. In Fig. 5 full triangulation of the cusp margins reduces the area bounded by these margins by 36.3 per cent. (Area of triangle subtracted from area of smaller circle and result expressed as percentage of latter.) It is not to be understood that this figure represents 36.3 per cent of normal, because, under normal conditions, there is probably some trigonoidation of the valves and hence the percentage loss of area in the above example is no doubt exaggerated. The same relationship would hold for trigonoidation as for triangulation, except that in the case of the former the loss of area is not so great. Probably it is never sufficient to have an obstructive influence. This diminution in cross-sectional area does explain one point, however, viz., the greater the dilatation the more easily is a murmur produced. Nevertheless, no matter what the degree of dilatation, if it is due to back pressure and this has been sufficient to lead to tricuspid incompetence, a pulmonary systolic murmur may not occur.

In general there are three groups of conditions in which a pulmonary systolic murmur may occur in association with structurally normal valves. These groups are as follows:

A. Conditions Which Cause Dilatation of the Pulmonary Artery by Increasing the Peripheral Resistance in the Pulmonary Circulation.— Physiological examples in this group are the pulmonary systolic murmurs which may occur during full expiration or during the Valsalva experiment (attempted forced expiration with the glottis closed). Examples of a pathological nature may be mitral stenosis, emphysema, extensive pulmonary fibrosis, and Ayerza's disease. In some cases of mitral stenosis the dilatation of the pulmonary artery may be so great that the semilunar valves become incompetent. Usually before this time the right ventricle has become pathologically dilated and has lost much of its systolic force, while the tricuspid valve has become incompetent. Because of these factors there may be no trigonoidation murmur.

B. Conditions Which Result in Stenosis and Therefore Proximal Dilatation of the Pulmonary Artery by Producing Kinking, External Pressure, or Traction Distortion of the Vessel or Its Main Divisions.— Under this heading may be placed the pulmonary systolic murmurs which not infrequently accompany pregnancy, obesity, ascites, and other forms of abdominal distention; occasionally extensive unilateral pleural effusions or pneumothorax; pulmonary fibrosis with mediastinal displacement; mediastinal tumors; extensive thoracoplasty, etc.

Of course, the stenosis itself may be responsible for a systolic murmur in these cases. Such a murmur is usually very loud and harsh as compared with a trigonoidation murmur.

C. Conditions Which Result in Increased Venous Return and Therefore Increased Stroke Volume and Increased Systolic Force of the Right Ventricle.—This is the most interesting group, and it accounts for the majority of trigonoidation murmurs. Obviously anything which increases the stroke volume and systolic force of the ventricles should favor the production of this type of murmur.

The common physiological example in this group is exercise, and the mechanism by which it causes an increased venous return is too well known to require discussion.

Arteriovenous aneurysm may be taken as an example of a purely pathological condition causing increased venous return.

Fever is another condition commonly associated with a pulmonary systolic murmur. In fever the basal metabolic rate increases, and there is need for increased elimination of heat. This is provided for by an increased minute output of the heart and a dilatation of the peripheral vessels. The basal metabolic rate increases by about 7 per cent for each rise of 1° F. However, Samson Wright[3] states that the main need increasing the cardiac output is probably not the change in metabolic activity, which is small, but the need for temperature regulation, and that the increase in venous return needed to maintain the raised minute output is presumably brought about by raised capillary and venous pressure resulting from the cutaneous arteriolar dilatation.

It follows from what has just been said that any condition which results in dilatation of the cutaneous arterioles and the necessity for increased heat elimination may result in the development of a pulmonary systolic murmur. Thus Norris and Landis[4] quote F. Howell to the effect that the vascular dilatation induced by prolonged sweat baths is of itself sufficient to cause the appearance of murmurs in the majority of cases.

In thyrotoxicosis there is a marked increase in the minute output of the heart and a corresponding increase in the venous return. The factor of venous return thus explains the basal systolic murmur of thyrotoxicosis.

Conditions which result in anemic and anoxic anoxemia result in an increase in the minute output and venous return as a compensating mechanism and may be accompanied by trigonoidation murmurs. There is probably no such thing as a "hemic" murmur per se, i.e., a murmur due to an alteration in the physical state of the blood itself.

There are two other common conditions which may be classified in this group, namely, excitement and the effort syndrome. These are often accompanied by a basal systolic murmur. They differ somewhat

from the other examples just given in that, in addition to an increased venous return, the systolic force is increased by heightened sympathetic tone. According to Samson Wright, emotional states produce varying degrees of elevation of the cardiac output. DuBois[5] quotes Grollman as having shown that psychic disturbances affect the cardiac output even more than the oxygen consumption. Grollman found in testing medical students that anger was associated with a rise of about 23 per cent in the cardiac output per minute but that worry over their standing in laboratory work caused somewhat smaller changes. Other work in psychoneurotic states has shown that these may be accompanied by a marked rise in cardiac output and therefore in venous return. It is quite possible that accelerated venous return in these cases is largely due to increased muscular tension.

Fig. 6.—Photograph of the pulmonary orifice of a heart which was fixed in a state of distention. In this preparation the valves are pushed back as far as they will go by a plug of cotton in the conus. The photograph demonstrates clearly what is meant by the term "trigonoidation." A point brought out in the preparation of such a specimen is that the sinuses behind the valves are the most distensible portions of the pulmonary artery, thus favoring the production of trigonoidation.

An important subject remaining for consideration is that of systolic murmurs arising at the aortic area in the presence of structurally normal valves. It is of course often difficult to say whether a certain basal systolic murmur originates at the pulmonary or the aortic orifice, because of transmission of the murmur. It is known, however, that pulmonary systolic murmurs are much more common as a whole than aortic systolic murmurs. Since it is felt that many aortic systolic murmurs, like most pulmonary systolic murmurs, are due to trigonoidation of the valve margins, it becomes necessary to explain why the aortic murmurs are so much less common. If one examines

the aorta and compares its qualities with those of the pulmonary artery, it will be noted that the former is thicker, offers considerably more resistance to distention, and proportionately has less maximal dilatability than the latter. The pulmonary artery, being a short structure of relatively small volume, requires considerable dilatability in order to accommodate the stroke volume of the right ventricle. The aorta, on the other hand, has great length and accommodates a large stroke volume with a relatively slight dilatation at any one point. If one will note the systolic expansion of the great vessels in the exposed heart of the dog, he will immediately see this point. The relative dilatabilities of the two great vessels can also be strikingly shown by cutting rings from them and stretching them with the index fingers. That trigonoidation murmurs are less common at the aortic than at the pulmonary orifice is due, then, to the relatively small dilatation of the aorta with each stroke volume of the left ventricle. At the pulmonary orifice most trigonoidation murmurs are due to physiological factors brought into play by normal or mildly pathological states such as exercise, excitement, fever, anemia, etc. These conditions are seldom sufficient to produce trigonoidation murmurs at the aortic orifice. Apart from dynamic dilatation of the aorta, most conditions which cause an aortic trigonoidation murmur are definitely, if not seriously, pathological, viz., hypertension, syphilitic aortitis, aneurysm of the ascending aorta, atherosclerosis, senile ectasia of the aorta, and coarctation. These conditions per se result in enough dilatation of the aorta that the addition of each systolic thrust is sufficient to produce trigonoidation and a murmur.

SUMMARY

Certain anatomical features of the great vessels and their valves are discussed.

Attention is drawn to the fact that basal systolic murmurs associated with structurally normal valves have a common factor in that they are connected with conditions which cause dilatation of the great vessels.

The association of systolic murmurs with dilatation of the great vessels is explained on the basis of physical changes in the relationship of the valve cusps to the lumen of the vessel. Experimental evidence has been given to corroborate this. The particular relationship of the valve cusps responsible for the murmur has been termed "trigonoidation."

An explanatory discussion is given of why various conditions such as exercise, excitement, anemia, thyrotoxicosis, etc., are associated with basal systolic murmurs.

The cause of the relative frequencies of pulmonary and aortic systolic murmurs is discussed and remarks made on their relative significance.

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Department of Clinical Reports

THROMBOANGIITIS OBLITERANS IN WOMEN

Report of a Case*

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New York, N. Y.

THROMBOANGIITIS obliterans is rare in women. Twenty-one cases have thus far been reported.[1-10] Herrell and Allen,[10] in a recent review, discuss the criteria for diagnosis in each of these patients. The following brief report is published to add to our meager knowledge of this condition as it occurs in women.

L. V., a Russian Jewess, aged forty-six years, was admitted to the Vascular Clinic of the New York Post-Graduate Medical School and Hospital on Nov. 27, 1934. Her history dated back one year, at which time she had exposed her bare feet to the floor of a cold room. Following this exposure, she noticed a burning sensation in the distal half of her left foot. The condition progressed, so that on admission she complained of a constant burning pain over the sole and medial aspect of her left foot. Moderate relief was afforded by heat, but the condition was greatly aggravated by cold. In the four months prior to admission, walking one block had produced an aching pain in her left foot and ankle, relieved only after a few minutes' rest. Two small ulcers had made their appearance beneath and between the last two toes of her left foot. Both of these ulcers were of four weeks' duration. One week prior to admission, she had noted a dull pain in her left hand and forearm, somewhat similar to the pain in the sole of her foot, but not so severe.

Her past history was essentially negative. In 1930 the fifth finger of her right hand had been amputated because of osteomyelitis associated with an acute infection. She had smoked on an average of eight cigarets a day since she was eight years of age. Rye bread was included in her daily diet, and she denied the use of alcohol.

Physical examination revealed a well-nourished and well-developed female. She was 59 inches (149.8 cm.) tall and 160 pounds (72.7 kg.) in weight. The blood pressure in millimeters of mercury was 130 systolic and 90 diastolic. General examination was essentially negative.

Examination of her extremities revealed a marked rubor of both feet, most prominent over the toes and inner aspect of her left foot. Pallor was present on elevation. The nail of the first toe of the left foot was greatly hypertrophied. Two small, moist ulcers were present under the toes of the left foot. The larger ulcer was located at the base of the fifth toe. Both feet were moderately cold. Examination of the extremities for pulsations revealed no pulsations in dorsalis pedis of either foot, nor in the posterior tibial or popliteal of the left leg. The right posterior tibial and popliteal were palpable. The radial and ulnar vessels of the left arm were not palpable. Both vessels could be felt in the right wrist. The oscillometric readings may be seen in Table I.

The routine complete blood count, blood sugar, urinalysis, and blood serology for syphilis were negative. The electrocardiogram was negative except for a rapid rate

*From the Vascular Clinic of the New York Post-Graduate Medical School and Hospital of Columbia University.

of 101. Roentgenograms of the lower extremities revealed no evidence of arteriosclerotic plaques. No abnormal changes were noted on examination of the eyes. Unfortunately, a Landis hot water immersion test was not performed on admission, but Table II shows the results of a test performed on Jan. 27, 1936. This would indicate the establishment of good collateral circulation, in view of the oscillometric readings, which were still as indicated in Table I.

TABLE I

OSCILLOMETRIC READINGS

	LEFT	RIGHT
Dorsali pedi (arch of foot)	0	0
Proximal to ankle	0	½° at 100 mm. Hg pressure
Distal to knee	1¾° at 100 mm. Hg pressure	2° at 100 mm. Hg pressure
Proximal to wrist	0	½° at 100 mm. Hg pressure

TABLE II

HOT WATER IMMERSION TEST*

TIME P.M.	RIGHT FOOT				LEFT FOOT				
	FIRST TOE	THIRD TOE	FIFTH TOE	DORSUM	FIRST TOE	THIRD TOE	FIFTH TOE	DORSUM	R. T.
1:00	Admitted to clinic for temperature stabilization								
2:00	32.0	32.6	32.5	33.3	28.9	30.1	29.2	30.3	26.6
2:29	31.1	32.0	31.3	32.5	30.6	28.9	28.9	31.3	19.1
	Arms submerged in water at 45° C.								
2:20	31.5	31.6	31.5	32.9	31.5	29.5	29.3	31.6	22.6
2:35	33.0	31.4	30.7	32.6	31.2	30.3	29.6	31.4	24.0
2:50	32.4	33.3	32.8	33.3	31.4	30.5	29.2	31.5	25.0
3:05	33.0	33.3	33.0	33.0	31.8	30.5	29.3	32.0	25.4

*Temperature readings in centigrade. Described by Landis.

Typhoid vaccine* was given intravenously, starting with a dose of 10 million and increasing the dosage gradually to 70 million. The dosage given produced a 2 to 3 degree rise in body temperature, without an initial chill. Both ulcers were completely healed after twenty-seven injections. Eleven additional injections were given, and the patient became symptom-free. During May, 1936, claudication and rest pain returned. Tissue extract 568,† 3 c.c., three times a week, was given intramuscularly, and after five injections the patient continued to have claudication, but no rest pain. Heart muscle extract,‡ 4 c.c., three times a week, was given intramuscularly, and, after nine injections, the patient was able to walk fifteen blocks without developing claudication. Twenty-six more injections were given, and the patient was discharged from the clinic. Since Sept. 12, 1936, the patient has been symptom-free.

DISCUSSION

We believe that we are justified in reporting this case with the diagnosis of thromboangiitis obliterans for the following reasons: (a) the patient is a Russian Jewess; (b) she was forty-five years of age at the

*Special typhoid vaccine (100,000,000 to 1 c.c.) supplied through the courtesy of Kirk Biological Laboratories, Bloomfield, N. J.

†Supplied through the kindness of Sharpe and Dohme.

‡Specially prepared and supplied through the kindness of Eli Lilly and Co.

onset of her symptoms; (c) there was no evidence of calcification to be seen in x-ray films of the affected extremities, taken for special study in that regard; (d) diabetes mellitus is not present; (e) she had smoked an average of eight cigarets a day from the age of eight years (thirty-seven years); (f) rye bread had been an important feature in her diet since infancy, much of which time was spent in Eastern Europe; (g) her pains were burning in character, and she had severe rest pains; (h) she also had claudication, as a residual symptom, after her ulcers healed; (i) her ulcers were deep, moist, located between the last two toes of the left foot and excruciatingly tender; (j) she had marked rubor on dependency and pallor on elevation; (k) there was widespread involvement of the peripheral arteries, as determined by absence of pulsations of the major arteries supplying both feet and the left hand; (l) there was prompt response to intravenous typhoid therapy, with healing of the ulcers, even though the patient was ambulatory.

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Department of Reviews and Abstracts

Selected Abstracts

Krebs, A.: The State of the Heart Following the Introduction of Radioactive Substances Into the Organism. Ztschr. f. Kreislaufforsch. 28: 701, 1936.

The author measured the concentration of radioactive substances in various organs obtained post mortem. The material was obtained from five patients who had been exposed in various ways to these substances. The author found that the heart had retained relatively little of these substances as compared with the other organs. This fact was confirmed in animal experiments. Dilatation of the heart which was found in some of these patients is attributed chiefly to the pulmonary hypertension and fibrosis which these substances cause, although a direct action cannot be ruled out.

L. N. K.

Wezler, K., and Böger, A.: The Influence of the Musculature of the Blood Vessels on the Arterial Pressure Dome. Ztschr. f. Kreislaufforsch. 28: 759, 1936.

The methods used have been described previously by the authors. The observations were made on living subjects. It was found that the volume elasticity modulus curves of the elastic and muscular arteries differ in slope even in the same person. Changes in the tone of the smooth muscles of blood vessels alter the arterial pressure dome. The apparent length of the pressure dome increases with elevation in mean blood pressure but to different degrees depending on the tonus of the vascular muscles. Such tonus changes also modify the volume elasticity modulus of the pressure dome. The main significance of the smooth muscle in the wall of the aorta is its tendency to keep the apparent elasticity coefficient of the pressure dome constant when the pressure within it is varied 50 mm. Hg or more. The authors suggest that reflexes from the root of the aorta and carotid sinuses may act not only on the heart and peripheral vessels, but also on the smooth muscle of the aorta to help keep the arterial pressure dome constant.

L. N. K.

Clark, Eliot R., and Clark, Eleanor L.: Observations on Living Mammalian Lymphatic Capillaries: Their Relation to the Blood Vessels. Am. J. Anat. 60: 253, 1937.

The regeneration of lymphatic capillaries has been studied by observation in "round table" chambers inserted into the ears of living rabbits. It has been established that new lymphatic capillaries grow by a process of sprouting from preexisting endothelium and that they form an independent system of vessels.

In the process of the development of blood capillaries, clear perivascular spaces may persist. These spaces occasionally acquire a border of longitudinally arranged connective tissue fibers resembling definite channels. When the lymphatic capillaries invade the areas around the blood capillaries before the dense intravascular tissue has

been formed, they sometimes follow the course of the blood vessels but frequently grow at random in the gelatinous intravascular substance. When the intravascular connective tissue is present the lymphatic vessel usually advances contiguous to the artery or vein. When the contiguous blood vessel is a capillary or thin-walled vein, direct leakage of fluid from the blood stream to the lymphatic vessel may occur.

Following periods of inflammation, localized areas of widening are observed in the blood vessel which accompanies the lymphatic vessel. This enlargement is relatively greater and persists longer on the side next to the lymphatic. At the time of active blood flow, the bulges in the wall of the blood vessel indent the wall of the accompanying lymphatic, encroaching on its lumen, while with decreased pressure in the blood vessel the "aneurysm" is inverted and the wall of the lymphatic then protrudes into the vein. If the endothelium of the blood vessel is weakened, hemorrhages may occur at the bulging place. However, no fistula was observed in any of the preparations.

Because of the sluggishness of lymph flow in peripheral lymphatics, cells which entered a lymphatic from a neighboring blood vessel frequently remain for hours or days within its lumen before moving on. Phagocytosis of degenerated polymorphonuclear leucocytes and of erythrocytes by macrophages occasionally occurs inside the lumen of the lymphatic capillaries. In those instances in which newly formed arteries have acquired active contractility, the accompanying lymphatic is compressed when the artery dilates, and expands when the artery contracts.

E. A. H.

Brückner, G.: A Measure of Cardiac Function. Ztschr. f. Kreislaufforsch. 28: 721, 1936.

The author recorded the venous pulse optically simultaneously with the electrocardiogram and the heart tones. He determined congestion on the basis of alterations of the systolic collapse of the venous pulse. He concluded that the alterations of this part of the venous pulse give the earliest signs of congestive heart failure, and this makes venous pulse registration of value in congestive failure.

L. N. K.

Fischer, R.: Clinical Studies of the Jugular Venous Pulse. Ztschr. f. Kreislaufforsch. 28: 801, 1936.

Stasis in the neck veins below the level of the jugular vein enhances the volume pulsations of the jugular vein. When this stasis exceeds an optimum, the pulsations in the lower part of the neck decrease and disappear but are still noticeable in the upper part of the neck. A large venous pulsation on the left rather than the right side of the neck is a sign of congestive heart failure. Similar significance is to be attached to a unilateral positive venous pulse or to a positive venous pulse occurring only in expiration. The distention of the neck veins with a disappearance of pulsations following pressure on the abdomen is also valuable in indicating stasis.

L. N. K.

Von Borisdorff, B.: Technic of Measuring Arterial Pressure Directly by Means of Arterial Puncture. Acta med. Skand. Suppl. 78. Report of 17th Scandinavian Congress of Medicine, June, 1935, p. 293.

The simple and known technic of arterial puncture under novocaine anesthesia was carried out. The needle was connected to a Broemser manometer through a three-way stopcock by a metal (lead) tube. A syringe half-filled with sodium

citrate solution was attached to the stopcock so that immediately after puncture the needle and adjacent portions of the apparatus could be filled with citrate solution.

The Broemser Frank manometer together with the source of light was mounted on a heavy metal rod, the other end of which was fixed to the camera stand. The rod could be moved vertically and horizontally and fixed tightly within a limited zone. The procedure was to have the rod so placed before puncture of the artery that the manometer with the lead tube projecting was not far from where the point of connection with the needle would be after the latter's insertion. The manometer and lead tube were filled with citrate and the connecting lead tube bent until its conical end could be thrust into the stopcock to which the needle was already connected. A little practice soon enabled one to place the manometer correctly before puncture. Since moving the manometer made necessary readjustment of the optical system, it was essential to have it placed beforehand within the region through which the lead pipe could be conveniently bent. The author issues an interesting warning, namely, that if one has to hunt for the artery and injures it in puncturing, the pulse may disappear. If this happens he recommends giving up the experiment. Very excellent records are shown of arterial pressure during injection of adrenalin and during a Valsalva experiment. Sample curves of two or three varieties of pulse are also reproduced.

J. M. S.

Wolffe, Joseph B., and Digilio, Victor A.: Pancreatic Extract (Tissue Extract No. 568): XIV. Its Use in the Treatment of Hypertension. J. Lab. & Clin. Med. **22**: 375, 1937.

The effect of de-insulinized pancreatic extract (tissue extract No. 568) has been studied in a series of 150 unselected cases of hypertension. One hundred patients of the group were used as controls. Blood pressure readings of the patients in bed were taken three times daily and of the ambulatory patients twice weekly. A total of 3,800 injections of tissue extract was given in this study. There were no unusual complications from the injections except slight pain at the site of the injection; mild urticaria in two patients, a sterile area of fatty necrosis in one, and a staphylococcic abscess in a diabetic patient.

In eight of 108 patients suffering from hypertensive cardiovascular disease, there was a marked lowering of systolic and diastolic blood pressure following the administration of the extract. In 62 per cent of this group symptomatic relief which persisted in some cases for over a year was obtained. There was no correlation between the symptomatic relief and the effect on the blood pressure. It is believed that the relief obtained is associated with metabolic changes, probably an improvement in the lipoid metabolism. In six of eight patients with essential hypertension without changes in the eyegrounds and without renal changes, a temporary lowering of the blood pressure was obtained which lasted only while tissue extract was being administered.

E. A. H.

Weicker, B., and Nehrkorn, O.: Myocardium and Tonsillitis. Ztschr. f. Kreislaufforsch. **28**: 633, 1936.

The electrocardiogram is the only certain diagnostic criterion of involvement of the myocardium in both acute and chronic tonsillitis. The evidence appears not only as A-V block and extrasystoles, but also as deformities in the various segments of the curve, especially the T-wave.

L. N. K.

Schlomka, G., and Raab, W.: The Significance of the Relative Duration of Systole—Its Relation to Age in Healthy Persons. Ztschr. f. Kreislaufforsch. **28:** 673, 1936.

On comparing the duration of electrical systole (the Q-T interval) with the cycle length in 336 normal resting subjects (having an average age of forty-three years) the author found that Fridericia's formula ($S = F \sqrt[3]{C}$) was applicable; F was found to be 8.02 ± 0.02 in this group instead of 8.22 as found by Fridericia and 7.57 as found by Herxheimer. An analysis showed that systole/cycle ratio increased as a person aged, the correlation factor F varying from 7.95 in youth to 8.30 in senility. This is a functional response to aging. In children, F was 7.00; and the short duration of systole in this age group, the authors argue teleologically, permits more time for diastole at the more rapid heart rates which are present in children.

L. N. K.

Brüner, H.: Blood Pressure and Pulse Recording With Electrical Transmission. Ztschr. f. Kreislaufforsch. **28:** 814, 1936.

A triode circuit is described in which both grid and plate are provided with a variable oscillatory circuit coupled by a mutual variable inductance. The plate current can drop in the region of resonance of the grid and plate circuits from a maximum to almost zero. One of the condensers in the grid circuit is constructed so as to permit small capacity changes when it is submitted to pressure changes. In this way pressure changes can cause changes in the plate current which can be recorded with an oscillograph. The entire circuit is modeled after one used in industry for measuring thickness of objects. (No description is given of the actual arrangement for connecting the measuring condenser to the animal).

A. K.

Kiss, P. v.: Diphtheritic Alterations of the Heart. Ztschr. f. Kreislaufforsch. **28:** 753, 1936.

This analysis is based on an experience with over 500 clinical cases of diphtheria seen by the author. As a result he divides diphtheritic heart involvement into a number of stages as follows:

1. The period of early changes—the period of cardiac dysfunction—which lasts three weeks and consists of the following subdivisions:
   a. The period of toxin invasion occurring during the first two or three days. No anatomical changes occur, and deaths are rare. There is fever, malaise, tachycardia, and an elevated blood pressure. It is a period of cardiac stimulation.
   b. This is then followed by a period during which anatomical changes develop in the heart and/or the conducting system. Hence, block and QRST deformities occur. Bradycardia is also present.
   c. This is then followed by a period in which the ectopic centers become overactive. Tachycardias and arrhythmias occur at this time and these may lead to dilatation, ventricular fibrillation, and death.
2. The period of late changes—the period of heart weakness—which lasts from the third to the eighth or the twelfth week. The heart shows fragmentation and myolysis and also evidence of interstitial inflammation. Clinically, there are the various manifestations of heart failure, and death, when it occurs, resembles that in other types of heart failure.

In diphtheria, in addition to the above, certain rarer complications occur such as emboli from cardiac thrombosis, endocarditis, and anaphylaxis from serum.

L. N. K.

Griffith, J. Q., Jr., Jeffers, W. A., and Lindauer, M. A.: Transient Hypertension in Rats Following the Extravascular Administration of Fluid. Am. J. Surg. **118**: 1, 1937.

A report has been made previously of experiments in which intracisternal injection of colloidal kaolin produced marked rise in cerebrospinal pressure and in blood pressure in the rat. Additional experiments are reported in which the effect on the blood pressure of increase in cerebrospinal fluid has been observed. An increased amount of cerebrospinal fluid can be produced by giving hypotonic fluids intravenously, but when blood pressure changes are to be studied, these fluids must be given extravascularly, either by hypodermoclysis or by intraperitoneal injection. A vascular hypertension appeared in 40.5 per cent of 129 rats given fluid, either distilled water or physiologic saline, in amounts not exceeding 30 c.c. per 100 gm. of body weight subcutaneously, or 15 c.c. per 100 gm. of body weight intraperitoneally. The hypertension thus produced was associated with increased cerebrospinal fluid pressure. A correlation with blood dilution or with increased water content of the brain could not be demonstrated. A difference is recognized in the experimental syndrome thus produced from that described by Rowntree because this syndrome can be produced either by physiologic saline, which never produces "water intoxication," or by water in relatively smaller amounts than that used by Rowntree. The animals did not appear to be very ill and seldom had convulsions.

E. A. H.

Tirala, L. G.: The Action of Deep Breathing Upon Blood Pressure. Deutsche Med. Wchnschr. **63**: 92, 1937.

By way of introduction the author states that he is unable to divide patients with hypertension, as he sees them in Southern Germany, into the varieties of "red" and "white" hypertension described in Northern Germany. Pale hypertensives have, in his experience, kidney involvement as well. He reports, inadequately, two cases of mild hypertension as examples of what can be done by deep breathing. Only systolic pressure is shown in the charts. In one case it drops from variations between 150 and 120 to between 110 and 90 mm. Hg, in the other, from 170 and 140 to between 140 and 120. Breathing exercises are given three or four times daily for six to eight minutes, and emphasis is placed chiefly upon expiration rather than inspiration because most of his patients' chests were fixed partly in the inspiratory position. The author believes that this mode of treatment is responsible for the disappearance of subjective symptoms such as dyspnea, insomnia, irritability, headache, poor memory, etc., and flatulence as well.

J. M. S.

White, James C., Okelberry, Alfred M., and Whitelaw, George P.: Vasomotor Tonus of the Denervated Artery; Control of Sympathectomized Blood Vessels by Sympathomimetic Hormones and Its Relation to the Surgical Treatment of Patients With Raynaud's Disease. Arch. of Neurol. & Psychiat. **36**: 1251, 1936.

Denervation of the sympathetic nerve supply to the arm by ganglionectomy has proved far less effective in relieving the symptoms of Raynaud's disease in the upper extremities than has a similar procedure in relieving the symptoms and restoring adequate circulation in Raynaud's disease of the lower extremities. The

reason for this discrepancy has been obscure until recently. A clue to the solution of the problem may be found in the phenomenon well known to physiologists, since the work of Elliott in 1905, that denervated smooth muscle becomes abnormally sensitive to epinephrine reaching it in the blood stream. The possible clinical significance of this principle was overlooked up to the time of the work of Freeman, Smithwick, and White in 1934. These investigators found that in human beings in whom cervicothoracic sympathectomy had been performed a striking vasoconstrictor response occurs both as a result of intravenous injection of very dilute quantities of epinephrine and as a result of stimulation of the adrenal glands by insulin-induced hypoglycemia.

In order to obtain further information concerning this constrictor response after sympathectomy, a series of experiments was performed on 35 albino rabbits and 3 monkeys. The extent of vasoconstriction in the rabbit's ear in response to cold, fear, psychic or painful stimuli was determined after the following procedures had been carried out: (1) acute denervation by infiltrating the tissue at the base of the ear with a 1 per cent procaine solution; (2) complete surgical sympathetic denervation of the ear including ganglionectomy with subsequent degeneration of postganglionic neurons; (3) surgical sympathetic denervation of the ear including ganglionectomy and resection of one adrenal gland and denervation of the other; (4) preganglionic sympathectomy of the ear by laminectomy and division of the upper thoracic spinal roots or by resection of the inferior cervical and first and second thoracic sympathetic ganglia. In the monkeys, similar tests were performed and adrenalin injection was done following cervicothoracic ganglionectomy and after anterior rhizotomy from the fourth through the tenth thoracic segment. In one animal the two procedures were carried out on opposite sides.

The results of the experiments demonstrate conclusively that the increase in sensitivity of the denervated arterial wall is much greater after ganglionectomy and degeneration of the postganglionic neurons than after destruction of the preganglionic portion of the vasoconstrictor pathway, with preservation of the ganglia. Some circulating hormone mediates the vasospasm which persists after ganglionectomy and degeneration of postganglionic fibers and it is thought to be adrenalin. Sympathin and other as yet unknown substances probably play a contributory rôle.

The difference in results from cervicothoracic ganglionectomy and lumbar ganglionectomy can be explained on the basis of the different anatomic arrangement of the vasomotor outflow to the arms than to the legs; according to Langley, "the vertebral sympathetic ganglia are segmental and each supplies sympathetic fibers to its own spinal nerve. The few fibers which do not arise from the corresponding ganglion arise from the ganglion next above or below." Therefore, lumbar ganglionectomy interrupts the vasoconstrictor outflow to the sciatic nerve in its preganglionic portion in contrast to the cervicothoracic ganglionectomy which causes degeneration of the postganglionic fibers to the brachial plexus. The importance of these experiments to clinical surgery is in emphasizing that the ganglia which are commonly removed in cervicothoracic ganglionectomy for Raynaud's disease are the most important ones to preserve. Section of the thoracic sympathetic chain below the third ganglion and resection of the proximal 2 to 3 cm. of the second and third intercostal nerves produces sympathetic denervation of the upper extremity of man without performing ganglionectomy. Theoretically, such a procedure would prevent the greatly increased sensitivity of arterioles to epinephrine which follows ganglionectomy. Consequently, the results of preganglionic sympathectomy for Raynaud's disease of the upper extremities should be as good as those following the standard type of sympathetic denervation for Raynaud's disease of the lower extremities. There is considerable evidence that this is true.

E. A. H.

Loeffler, Louis: Genesis of Intestinal Infarction Following Embolization of the Superior Mesenteric Artery. Arch. Path. 22: 755, 1936.

One would expect that embolic occlusion of the superior mesenteric artery in man would result in anemic necrosis of the intestine, but it is well known that it causes a hemorrhagic infarct. Numerous investigators, attempting to obtain an explanation, have ligated superior mesenteric arteries in animals. Contradictory results have been obtained. The author ligated the superior mesenteric arteries of rats, immediately and thereafter observed the blood vessels in the intestine, and observed an immediate arrest of the whole circulation except in the few collateral channels. Anemic necrosis resulted. The collateral channels are extraordinarily few and completely unconcerned with the process of infarction. After ligation of the portal vein as well as of the superior mesenteric artery, the collateral circulation is more extensive. Likewise, thrombosis of an intestinal vein or strangulation of an intestinal loop—measures which increase venous pressure—results in hemorrhagic infarction. The author reasons that the cause of the clinical hemorrhagic infarction found in embolization of the superior mesenteric artery is to be sought in the congested and altered state of the circulation caused by cardiac changes which produce the emboli.

H. M.

Spiegel, Rose: Clinical Aspects of Periarteritis Nodosa. Arch. Int. Med. 58: 993, 1936.

Because of the variability of symptoms, periarteritis nodosa mimics other conditions and even with the aid of biopsies has been diagnosed correctly in only about 12 per cent of the proved cases. In recent years diagnoses have been much more accurate, because with such multiplicity of symptoms no other single diagnosis is applicable.

Fifteen cases of periarteritis nodosa with post-mortem studies are presented. More than half had prodromal illnesses—acute tonsillitis, acute sinusitis, scarlet fever, or sensitization asthma. Four clearly had had rheumatic fever. The usual mode of onset was with abdominal pain, associated with articular, cardiac, or renal symptoms. All the patients showed cardiac and renal involvement at autopsy. Twelve had cutaneous lesions of various sorts; 12 had polyserositis; 7 had surgical complications involving the gastrointestinal tract, 3 of which were hemorrhagic pancreatitis; 5 had arteritic lesions of the liver; one had periportal fibrosis; and 2 had fatty degeneration. No one cause of periarteritis nodosa has been found. The periarteritic nodules are small aneurysms, but no case has been proved to be caused by syphilis. Attempts to reproduce the disease in lower animals by inoculation of crushed nodules have been inconclusive. The bacteria principally implicated in the prodromes of periarteritis nodosa are the hemolytic streptococci. The disease may be a superimposed vascular reaction in the course of rheumatic fever. Healing can occur. Healed periarteritic lesions closely resemble arteriosclerosis.

H. M.

Gutzut, R.: Gangrene From Blocking of the Veins. München. med. Wchnschr. 83: No. 40, 1936.

After a lengthy introduction which begins with Harvey's discovery, which follows the increasing emphasis placed upon the vascular system instead of upon the heart alone, and which ends with the statement that the importance of the veins is not yet fully appreciated, the author reports six cases of venous thrombosis. The striking facts common to all save one of the cases were that they occurred suddenly and produced moist gangrene (usually with edema), that the pulsations of the artery

could not be felt, that they were taken to be cases of arterial embolism. That the artery was not occluded was ascertained by operation or autopsy. He states that a reliable means of distinguishing between venous and arterial blockage is surface temperature—in the former the temperature is normal provided gangrene is not already present. Figures for the surface temperatures are not given, however.

J. M. S.

Hunt, John H.: The Raynaud Phenomena; A Critical Review. Quart. J. Med. 5: 399, 1936.

A critical review of the Raynaud phenomena is presented. The differential diagnosis of the various conditions in which these phenomena occur is considered in detail. The probable explanation of the mechanism producing the symptoms and signs and the results from sympathetic ganglionectomy are discussed.

E. A. H.

McKechnie, R. E., and Allen, E. V.: Sudden Occlusion of the Arteries of the Extremities. Surg., Gynec. & Obst. 63: 231, 1936.

The sources and causes of embolus and thrombosis of the peripheral arteries are discussed. In 47 per cent of the cases, the symptoms appeared suddenly and reached their maximal intensity quickly; in the remaining cases the development of symptoms was gradual, requiring from one hour to several hours to reach full development. In only 54 per cent of cases was pain the initial symptom. The incidence of diagnosis of sudden arterial occlusion parallels roughly the suspicion by the physician that it exists. If one examines the extremities for the condition only when severe pain, pallor, and coldness exist, many cases will be overlooked. Thrombophlebitis is the only condition which may be differentiated with difficulty from sudden arterial occlusion. Ordinarily the normal temperature, edema, distended veins, and normal arterial pulsations observed in cases of thrombophlebitis serve as an adequate contrast to the lowered temperature, collapsed veins, and diminished or absent pulsations in the arteries in cases of sudden arterial occlusion. However, arterial pulsations may be absent temporarily in phlebitis, apparently as a result of spasm. In sudden arterial occlusion the veins may be distended, usually after many hours have elapsed, as a result of secondary venous thrombosis. Under such circumstances close attention must be given to the mode of onset and the known possibilities of embolism. In rare instances the diagnosis may not be clear until many hours have elapsed.

The probability that arterial spasm is responsible for the pain in embolism either directly or as a result of the ischemia it produces is so logical and fits so well with recorded observations regarding suddenness of onset, severity, and the difficulty of localizing the pain that there appears to be a distinct cause and effect relationship.

There are three important "don'ts" in the treatment of sudden arterial occlusion: Don't delay treatment for more than two or three hours; don't elevate the extremity; and don't subject it to heat which exceeds by more than a few degrees the temperature of the body. Delayed treatment means a poor prospect of recovery in those instances in which recovery would not occur spontaneously. Until the custom disappears entirely, it cannot be emphasized too frequently that tissue deprived of its normal blood supply does not tolerate heat well. Hot water bottles are frequently of a temperature which exceeds 150° F. The extremity should be placed in a dependent position. When the legs are involved the head of the bed should be elevated; when the arms are involved, the patient should be in the semisitting position. Vasodilators should be given to relieve arterial spasm, if present. The use of intermittent negative and positive pressure has been very successful in some hands and should

be used if a machine is available. On the assumption that one of the chief requisites for a favorable outcome is the induction of collateral arteries to assume a heightened function of transportation of blood, spinal anesthesia may be tried when the lower extremities are involved. Brachial plexus block may produce similar effects in the upper extremities. General anesthesia may be used if the condition of the patient permits, for the same reason that spinal anesthesia may be of value. Sympathectomy, likewise, produces maximal vasodilation and is of value in sudden arterial occlusion, as shown experimentally, but ordinarily the condition of the patient does not warrant such a major operation. If the procedures outlined, exclusive of sympathectomy, do not produce a rapid improvement in the circulation, surgical removal of the clot should be considered when occlusion is due to an embolus.

E. A. H.

Allen, E. V., and Lauderdale, T. L.: Accidental Transmission of Thrombo-Angiitis Obliterans From Man to Man. Proc. Staff Meet., Mayo Clin. **11**: 641, 1936.

A surgeon, a Scotchman, forty-five years old, who had been well except for pulmonary tuberculosis, had smoked forty cigarettes daily for twenty-five years. He had never had superficial phlebitis. Six months previously, while he was amputating the toe of a thirty-six-year-old man with thromboangiitis obliterans, a spicule of bone from the patient's toe had accidentally pierced the flesh of the palmar surface of the third finger of his right hand. No local reaction occurred subsequently. One month later, color changes, consisting of cyanosis and pallor on exposure to cold and after wearing a rubber glove, had appeared on the third finger of the right hand, and three weeks later similar color changes had appeared on the fourth and fifth fingers of the same hand. Since then symptoms had diminished gradually but had not disappeared entirely.

Examination six months after the accident disclosed evidence of pulmonary tuberculosis, normal pulsations in the radial, ulnar, femoral, popliteal, dorsalis pedis, and posterior tibial arteries, reduction of temperature of the skin of the third, fourth, and fifth fingers of the right hand and markedly abnormal pallor of these fingers when the hand was elevated. Cervical rib could not be demonstrated by clinical or roentgenological examination. Thermometric studies revealed the temperature of the skin of the third, fourth, and fifth fingers of the right hand to be approximately 30° C., whereas that of the corresponding fingers of the left hand was approximately 35° C. Following the ingestion of 1 ounce (30 c.c.) of ethyl alcohol, the temperature of the skin of the fingers of the right hand increased to 34° C. and that of the corresponding fingers of the left hand, to 36.5° C. A diagnosis of thromboangiitis obliterans involving digital arteries of the right hand was made.

Raynaud's disease was satisfactorily excluded by the unilaterality of symptoms, pallor of the fingers on elevation, failure of arterial relaxation following the ingestion of alcohol, and the sex of the patient. Roentgenologic evidence of cervical rib was lacking. The possibility of the coincidental development of thromboangiitis obliterans of the digital arteries without there being a cause and effect relationship between the accident and the disease is almost certainly excluded by evidence of primary development of an occlusive arterial lesion in the injured finger and the absence of arterial lesions elsewhere in the body. There seems to be no other logical conclusion than that the agent responsible for the occlusive arterial lesion in the digital arteries of the patient was carried to the third digit of the right hand on the spicule of bone from the toe of a patient who had an occlusive arterial lesion.

AUTHOR.

Müller, A.: Mechanical Basis of the Regulation of the Circulation. Schweiz. med. Wchnschr. 65: 339, 1935.

An attempt is made to apply mathematical concepts of hydraulics to the problems of the circulation.

L. N. K.

Hochrein, M., and Matthes, K.: Circulation in Sport. Arzt und Sport, No. 19, 91, 1935.

The authors analyze the circulatory regulation in sport activity in which short and protracted effort are involved. They emphasize the value of the electrocardiogram in investigating the adequacy of the coronary circulation in such sport activities and of vital capacity measurements as an index of uneconomical blood distribution. Oxygen saturation determinations with Matthes method was also found to be valuable in determining how far the circulatory and respiratory adjustments met the work load of the exercise. The combination of these methods may be useful in determining weakness of the heart.

L. N. K.

Hartmann, H., Orskov, S. L., and Rein, H.: The Reaction of the Renal Vessels During the Course of Regulatory Events in the Systemic Circulation. Arch. f. d. ges. Physiol. 238: 239, 1936.

By means of Rein's thermoelectric stromuhr, the blood flow through one or both kidneys of dogs, or through one kidney and leg, and arterial pressure (femoral or carotid) were simultaneously recorded. The conclusions in each case based on nearly one hundred observations upon twenty-five dogs are direct. In general, it appears that the blood vessels of the kidney not only do not participate in systemic vascular reactions but vary in state of contraction to offset general reactions—that is to say, to maintain blood flow through the kidney constant in spite of changes in systemic pressure and flow. The blood flow through the kidney does not change (except perhaps for a small passive increase) when systemic blood pressure rises following closing of the carotid artery central to the carotid sinus, a pressor stimulus, but it decreases when a similar rise in systemic pressure is induced by inhalation of a mixture of gas containing 10 per cent carbon dioxide. Although the blood flow through the kidneys falls, naturally, on stimulation of the peripheral end of the vagus sufficient to stop the heartbeat temporarily, a compensatory dilatation of the renal vessels takes place which allows return of the blood flow to normal at a time when systemic pressure is still exceedingly low. Furthermore, if stimulation of the vagus is gentle, it can be inferred by various time relations that the compensatory renal vasodilatation is dependent upon the reduction in blood pressure and not upon stimulation of the vagus. It is shown that fifty to one hundred times the dose of adrenalin necessary to elicit vasoconstriction in muscle and skin is needed to constrict the renal vessels to a degree sufficient to reduce the flow of blood. The increased sensitivity of the denervated kidney to adrenalin is demonstrated. The authors are inclined to believe that the increased sensitivity is due to removal of a reflex vasodilatation. This view is suggested apparently because time relations between change of systemic blood pressure and decrease in blood flow to the kidney coincide in the ennervated kidney but fail in the denervated one. It appears that vascular reactions peculiar to particular regions, such as the kidneys, exist. That blood flow through the kidney tends to remain constant in spite of systemic pressure and flow changes finds ready application to an understanding of the behavior of kidney function observed in the clinic.

J. M. S.

McCombs, Robert P., and McElroy, James S.: Reversible Autohemagglutination With Peripheral Vascular Symptoms. Arch. Int. Med. **59**: 107, 1937.

Five of these patients had blueness of the peripheral parts and numbness on exposure to cold. The authors present a case in which symptoms of peripheral vascular insufficiency appeared on exposure to cold and subsided on warming. Autohemagglutination in vitro occurred at 27° C. The authors believe that the symptoms are caused by intravascular plugging resulting from agglutinated cells. The evidence for this is that local heat relieved symptoms promptly but heat applied elsewhere to the body failed to relieve symptoms in the affected limb or to raise skin temperature. The arms were immersed in water at 43.3° C., and the temperature of the skin in the lower extremities was recorded. Apparently they warmed the arms for only twenty minutes; a longer period would make the evidence even more convincing.

H. M.

Vires, J., May, P., and Balmis, J.: Concerning a Case of Erythromelalgia. Arch. Soc. sc. méd. et biol. **17**: 408, 1936.

In the right arm and hand of a fifty-nine-year-old miner attacks of pain, redness, and tingling increased by warmth and by hanging down had been occurring for about three weeks. The authors state that the red blotchy appearance during an attack and the manner in which the attacks occurred were very similar to the disease described by Weir Mitchell. X-ray photographs showed a destructive lesion of the cervical vertebrae and some of the disks with exostoses. These lesions were thought therefore to be due to chronic arthritis for which roentgen therapy of the shoulder region was given. Following treatment the whole syndrome disappeared. They attributed the symptoms therefore to irritation of the cervical sympathetic nerves and consequent vasomotor disturbances.

J. M. S.

Errata

In the article, "Heart Disease in Children," by Irving R. Roth, M.D., Claire Lingg, M.A., and Alice Whittemore, A.B., New York, N. Y., which appeared in the January issue of the JOURNAL, on page 52, line 3, the sentence should read, "Among the 149 first recurrences (Fig. 10*A*) polyarthritis was present, alone or combined, in 74 per cent (110 cases)" instead of, "Among the 94 second recurrences. . . ."

Also in line 5 of the footnote on page 38 the name "Mrs. Henry F. Glazer" should be "Mrs. Henry S. Glazier."